X-RAY ANALYSIS OF GRISEOFULVIN AND OTHER COMPLEX ORGANIC MOLECULES

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PREFACE

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Mrs. J.B. Barbour undertook the onerous task of typing the manuscript and I wish to record my appreciation here.

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S U M M A R Y

This thesis is concerned with x-ray structure determinations of complex organic molecules. In each case the phase problem has been surmounted by application of the heavy-atom method. The various analyses have been taken to different degrees of completeness.

In the first chapter is given a very brief theoretical account of the subject paying particular attention to the techniques employed in the course of this work.

The analysis of griseofulvin, in the form of its 5-bromo-derivative, was undertaken in order to define the stereochemistry of the molecule the structure of which was already known. Despite some difficulties encountered due to the presence of false symmetry in space group $P2_1$, the problem has been solved. Least squares refinement has reduced the discrepancy, R, to 14.0%.

A study of the conformation of the bicyclo (3,3,1) nonane system was undertaken using 1-p-bromobenzenesulphonyl-oxymethyl-5-methylbicyclo (3,3,1) nonan-9-ol. The results show that this system rather surprisingly adopts the twin-chair form. The chairs are, however, rather distorted by a flattening of the rings at the C(3) and C(7) positions. The structural parameters have been refined to a discrepancy,

R, of 12.9% by least squares methods.

Structural studies have been made on the bitter principle, simarolide, using both the m-iodobenzoate and 4-iodo-3-nitrobenzoate derivatives. When this work was commenced very little was known about the structure, but the complete constitution and stereochemistry of the molecule have been obtained, the absolute configuration being determined by examination of the anomalous dispersion of copper radiation by iodine atoms. Simarolide has been found to be a triterpenoid compound of the euphol type. Refinement of the structures has been retarded due to the difficulty of locating included molecules of solvent of crystallisation. The interim values of the discrepancies for the two derivatives are 21.6% and 24.1%, respectively.

The final chapter of this thesis describes a rather unsatisfactory structure analysis of a chromium carbonyl adduct of a compound produced by the reaction between diphenylketen and ethoxyacetylene. The crystallographic results obtained are in agreement with those found by conventional chemical and spectroscopic methods, but it has not yet been possible to refine the structural parameters to yield a better R-factor than 29.5%

C O N T E N T S

PART III

THE CONFORMATION OF THE BICYCLO (3,3,1) NONANE SYSTEM: X-RAY ANALYSIS OF 1-p-BROMOBENZENESULPHONYLOXYMETHYL-5-METHYLBICYCLO (3,3,1) NONAN-9-OL

PART IV

THE STRUCTURAL AND STEREOCHEMICAL DETERMINATION OF SIMAROLIDE

P A R T I

A BRIEF SURVEY OF SOME METHODS OF X-RAY DIFFRACTION ANALYSIS

1.(1). Introduction.

1912 is perhaps the most important date in the history of the development of x-ray crystallography. Prior to this it had not been established whether x-radiation was corpuscular or undulatory in nature. In addition, very little was known about the internal arrangement of atoms, ions or molecules in crystalline matter. In that year, however, Von Laue and his co-workers performed an important experiment which has had the most far-reaching consequences.

Since the roughly calculated interatomic distance in crystals (1Å) was of the same order of magnitude as the wavelength of x-rays (assuming them to be a wave-motion) Von Laue argued that it might be possible to obtain an effect analogous to that observed when visible light is passed through a diffraction grating. That the x-ray beam was indeed diffracted by the crystal lattices of copper sulphate pentahydrate and zinc blende proved that the radiation was of an undulatory character and opened up the field of x-ray crystal structure analysis.

The angles of diffraction obtained from the lattice yield the required data concerning the size and shape of the unit cell. The diffracted beams (or 'reflections' as they are colloquially called) may be recorded photographically using any of a variety of x-ray goniometers. It is found that these reflections fluctuate in intensity. From a

consideration of the distribution of these intensities it may be possible directly or, more usually, indirectly to obtain the atomic arrangement present in the crystal.

The structure analysis of organic compounds may be undertaken for either or both of two principal reasons:
1. To elucidate the molecular constitution of a compound which is either wholly or partially insoluble by the methods available to organic chemists. As will be seen later it is possible to establish not only the stereochemistry and the conformation which the molecule adopts, but also the absolute configuration in certain favourable circumstances.
2. To obtain fairly exact interatomic bond lengths, bond angles and non-bonded distances. This field is an extremely important one as the results can be correlated with theoretical values obtained by the methods of Quantum Mechanics. Obviously experimental values are required if the theory of the chemical bond is to progress.

One of the central difficulties which confronted crystallographers in the past was the vast amount of necessary calculations which were both laborious and time-consuming. In fact, prior to 1950, very few complete three-dimensional analyses of complex organic molecules were attempted. Since then, however, with the advent of high-speed electronic digital computers, the processes of calculating have been enormously accelerated.

One very real problem, however, still does exist in the field of crystal structure analysis.

The actual value of the intensity of any one reflection (hkl) depends on a variety of criteria, chief among which is a term called the structure factor, F(hkl). This, in turn, is related to both the direction of the diffracted spectrum and the distribution of scattering material in the unit cell. The structure factor, F(hkl), gives a measure of the scattering power of one unit cell in the crystal in the direction defined by (hkl), relative to that which would be obtained from a single electron under the same experimental conditions. In general F(hkl) can be portrayed as a complex number characterised by a structure amplitude $|F(hkl)|$ and a phase angle, α. The structure amplitude can readily be obtained from the value of the corresponding intensity, but, in the process of recording the intensity, the phase angle is inevitably lost. This unfortunate experimental fact constitutes the Phase Problem.

Bragg (1915) pointed out that, since a crystal was triply periodic, the electron density could be evaluated by means of a three-dimensional Fourier Series. The coefficients of this series, however, have to be the above-mentioned structure factors which, of course, are indeterminate in the absence of knowledge of the phase angles.

Various methods of circumventing this problem have now been evolved. Principal among these are the trial and error method which is applicable where the structure is simple and of known constitution; the isomorphous substitution method, where the phase is determined by consideration of the difference in scattering produced by an interchangeable pair of atoms in isomorphous compounds; combination of structure factor signs in centrosymmetric cases and the application of equalities and inequalities for large structure factors. These mathematical methods make use of the physical criteria that the electron density is nowhere negative and that atoms have spherical electronic distributions.

The technique which has been employed in phase determination throughout the work described in this thesis is the heavy atom method involving a simple application of the Patterson function. This will be described in more detail.

1.(2). The Phase Problem and the Heavy Atom Method.

Patterson (1934, 1935) developed a new function which was similar to the Fourier series for electron density calculation, but which used the squares of the structure amplitudes as coefficients instead of the first power terms. This enabled him to disregard phases. It follows that it

is always possible to compute the Patterson function, which can be expressed as:-

$$P(u,v,w) = V\int_0^{'}\int_0^{'}\int_0^{'} \rho(xyz)\rho(x+u,\ y+v,\ z+w)\ dxdydz \quad \ldots\ldots \quad (1.1)$$

or

$$P(u,v,w) = \frac{1}{V}\sum_{-\infty}^{+\infty}\sum\sum |F(hkl)|^2 \cos 2\pi(hu+kv+lw) \quad \ldots\ldots\ldots \quad (1.2)$$

In this expression V is the volume of the unit cell and $\rho(x+u,\ y+v,\ z+w)$ represents the distribution of scattering matter about the point (xyz) expressed in terms of u, v and w, and is similar to $\rho(xyz)$ but shifted from (xyz) by the quantities u, v and w respectively. P(u,v,w) will evidently be large when both the electron density distributions are appreciable and this is the situation which will obtain if an atom is situated at both (xyz) and (x+u, y+v, z+w). Consequently, every pair of atoms in the unit cell will give rise to a 'peak' in the Patterson map and the function represents a complete picture of all interatomic vectors.

One difficulty that is immediately apparent is the very large number of vectors which will result from all but the very smallest molecular structures. All vectors radiate from the origin and it can easily be shown that, in the case where there are N atoms in the unit cell, there will be N peaks superposed on the Patterson origin and a further

$\frac{N(N-1)}{2}$ independent maxima scattered throughout the unit cell.

When dealing with Patterson projections overlap leads to serious difficulty. Even three-dimensional synthesis is of limited application when the number of vectors is large, although Harker (1936) has pointed out that space group symmetry conditions give rise to specific vector peaks on definite line or plane sections through the unit cell.

Consideration of equation (1.1) shows that if only a few values of both $\rho(xyz)$ and $\rho(x+u, y+v, z+w)$ could be arranged to be very much greater than all the other terms it would be possible to obtain a few very prominent peaks in the Patterson distribution. Now this is exactly the situation which arises if, in the unit cell, we have a small number of atoms whose atomic numbers are considerably greater than those of all other atoms present. Since u, v and w are very simply related to x, y and z, it is possible to evaluate the coordinates of the 'heavier' atoms.

From the coordinates of the heavy atoms it is possible to evaluate phase angles for each reflection. These phase angles (α_H) will be fairly close approximations to those of the substituted molecule as a whole (α) since the heavy atom contribution to the phases dominates that due to the lighter atoms.

It is then possible to compute an electron density Fourier summation using the experimental structure amplitudes and the α_H values. The expression involved is:-

$$\rho(xyz) = \sum_{-\infty}^{+\infty} \sum \sum \frac{|F(hkl)|}{V} \cos\left(\frac{2\pi hx}{a} + \frac{2\pi ky}{b} + \frac{2\pi lz}{c} - \alpha_H(hkl)\right) \quad \ldots\ldots\ldots (1.3)$$

From the resulting map, which is contoured by joining up points of equal electron density, it should be possible to discern an approximation to the true chemical structure. The coordinates of recognisable atoms can be calculated and then used along with those of the heavy atom in a second phasing calculation. These new phase angles should be a closer approximation to reality and a further Fourier map should reveal a clearer picture of the molecular skeleton. This iterative process is continued until the structure analysis is complete.

This is the so-called heavy-atom method of phase determination which was first successfully applied by Robertson and Woodward (1940) in their solution of the structure of platinum phthalocyanine.

It is generally possible to introduce one or more heavy atoms into an organic molecule by conventional chemical methods if such an atom is not already present in the structure.

It is appropriate to add a short note as to the relative efficacy of heavy atoms as phase determiners. There are two particular cases to be considered.

(a) The Centrosymmetrical Case.

In this particular case the choice of phase angles is restricted to 0 and π in angular measure. This is equivalent to saying that the Fourier coefficients have either a positive or negative sign.

$$\rho(xyz) = \sum_{-\infty}^{+\infty} \sum \pm \frac{F(hkl)}{V} \cos 2\pi \left(\frac{hx}{a} + \frac{ky}{b} + \frac{lz}{c}\right) \ldots\ldots (1.4)$$

A suitable heavy-atom derivative is one in which the true sign is allotted to a large proportion of the structure amplitudes from the phasing calculation based on the coordinates of the heavy atom alone.

Sim (1957, 1961) has shown that a simple expression can be used to evaluate the number of structure factors, F, which have the same sign as the heavy atom structure factor, F_H, due allowance being made for the number and types of atom present in the unit cell:

$$r = (\sum f^2_H / \sum f_L^2)^{\frac{1}{2}} \ldots\ldots (1.5)$$

In a general case of a molecule including one heavy atom in a non-special position in a triclinic cell he shows that between 80 and 90% of the signs can be correctly determined as r varies from 1 to 2.

Woolfson (1956) has suggested that a weighting scheme be used to minimise errors in electron-density computations resulting from the wrong apportionment of some signs by the heavy atom.

Lipson and Cochran (1957) have pointed out that it is inadvisable to have a situation in which $\sum f_H$ is very much greater than $\sum f_L$, since then the heavy atom would tend to 'swamp' the lighter atoms in the resultant Fourier map, thereby rendering structure analysis much more difficult. They recommend unity as an ideal value for r.

(b) The Non-Centrosymmetrical Case.

In this circumstance the phase angles are free to have general values. Thus, instead of having the majority of the phase angles correct and a few wrong as in section (a), there is now a continuous distribution of errors some of which may be almost negligible and others very large.

Sim (1957) shows that this distribution is again a function of $(\sum f_H^2 / \sum f_L^2)^{\frac{1}{2}}$. The error in phase angle $\alpha - \alpha_H$ can vary between $\pm 180^\circ$. He uses the same general case as in (a) and demonstrates that when r = 1, 38% of the errors lie within $\pm 20^\circ$ of α and that this fraction increases to 67% when r = 2. The resolution of unknown lighter atoms is less propitious in the non-centric case and he shows that a weighting function analagous to Woolfson's based on the probable magnitude of phase angle errors can be employed to good effect.

Since, in the centro-symmetrical case the choice is merely between a positive and a negative sign compared with the gradual reduction of the phase angle error in the non-centric case, it is obvious that complete phase determination is a much faster process in the former category.

1.(3). Refinement.

After a structure is completely determined, an attempt is generally made to obtain the best possible atomic positions, by adjusting the coordinates of atoms by small amounts. This is equivalent to improving the phase angles and thus the agreement between observed and calculated structure amplitudes. This process is called refinement.

It is convenient to have some index by which the measure of agreement between $|F_o|$ and $|F_c|$ can be indicated. The expression

$$R = \frac{\sum \left| |F_o| - |F_c| \right|}{\sum |F_o|} \quad \text{---- (1.6)}$$

is the most frequently used equation. R is variously known as the residual, the reliability index, the agreement index, or - expressed as a percentage - the discrepancy. Evidently, during the process of structure analysis and refinement, R should be always decreasing.

There is a grave danger of placing too much reliance on a falling R-value. It is possible, especially when a phase-dominating heavy atom is present, that there are a considerable number of very poor agreements being masked by an apparently satisfactory overall discrepancy. The importance of examining the individual agreements should not be underestimated and the R-value taken only as a rough but useful guide in concluding whether adjustments of atomic parameters are improving the structure.

Various methods of refinement are available to the crystallographer and those used during the course of this work will be summarised briefly.

i) Fourier Methods.

It is possible to refine crystal structures by the simple expedient of using a Fourier Series in an iterative process viz. new atomic coordinates are calculated from an electron density distribution; these are used in a phasing calculation and then a further Fourier map computed and so on.

Examination of equations such as (1.3) shows that the true electron density is represented by an infinite series. In practice, the number of terms which can be included in such a summation is severely limited, the number being determined by the wavelength of the incident radiation. This effect is especially deleterious if the Fourier coefficients are still relatively large when the data are

cut off. The result of this is that false detail, meaningless negative electron density and diffraction 'ripples' surrounding true peaks show up on the Fourier map. This last phenomenon is a particularly serious one as it displaces peaks from their true positions. This is called the termination of series error.

Booth (1946) proposed a method of avoiding this difficulty. Two Fourier series using the same (hkl) terms are computed, one using observed structure amplitudes (F_o) as coefficients and the other the calculated structure amplitudes (F_c). Since series-termination errors are always present, it follows that the atomic coordinates calculated from these two maps will differ to a slight extent. These small deviations, $(x_o - x_c)$ etc. will give the size of the shifts to be applied to the original atomic coordinates. The accuracy of this method depends on the preciseness with which atomic scattering factors are known and on the fact that the postulated atomic arrangement must be strictly correct.

An equivalent procedure to Booth's method is called the difference or $(F_o - F_c)$ synthesis which has been discussed by Cochran (1951). In this approach the residuals, $(F_o - F_c)$, for each term are applied as Fourier coefficients in the normal manner. If the known atomic positions are superimposed on the map then the direction of shift is that

of the steepest contour ascent. The difference synthesis is also valuable for the alteration of temperature parameters; a negative value of $(\rho_o - \rho_c)$ at an atomic site indicating that an increase in temperature factor is required and vice versa.

The method has also been used in order to locate electron distribution directed along chemical bonds (Brill, 1950) and to establish the location of hydrogen atoms in relatively simple molecules as demonstrated in the analysis of anthracene by Cruickshank (1956).

An $(F_o - F_c)$ series, under the heading of error synthesis, was employed by Crowfoot et al. (1949) in their analysis of sodium benzylpenicillin. They point out that this form of synthesis avails itself most of the information that certain reflections are weak or absent, since then it is clear what the sign of the discrepancy between F_o and F_c is.

An obvious drawback to Fourier methods of refinement is that all F_o's are not measurable with the same accuracy. Apart from some which will be systematically erroneous due to extinction and absorption effects, there will always be random inaccuracies in the data.

ii) The Differential Fourier Synthesis.

This method was first introduced by Booth (1946a) and involves the evaluation of the first differentials of electron density around points in the unit cell where atoms are known to lie. At the true peak maxima these differentials will be zero and the problem is to find the small displacements of the atoms at any stage of refinement from these maxima.

Three equations are derived of the form

$$\frac{\partial \rho}{\partial x} + \frac{\partial^2 \rho}{\partial x^2}\epsilon_x + \frac{\partial^2 \rho}{\partial x \partial y}\epsilon_y + \frac{\partial^2 \rho}{\partial x \partial z}\epsilon_z = 0 \quad \ldots\ (1.7)$$

and from these by simultaneous solution can be obtained the quantities ϵ_x, ϵ_y, and ϵ_z, the deviations of the atomic coordinates from their true positions.

It has been shown that the calculations can be greatly simplified if the atoms concerned are assumed to be spherically symmetrical. In this circumstance using orthogonal axes expressions such as $\frac{\partial^2 \rho}{\partial x \partial y}$ become zero and the deviations simplify to equations such as

$$\epsilon_x = -\frac{\partial \rho}{\partial x} \Big/ \frac{\partial^2 \rho}{\partial x^2} \quad \ldots\ (1.8)$$

The differential synthesis method of refinement is subject to the same kind of errors inherent in the F_o synthesis, except that in the former case it is unnecessary to locate the atomic maxima by interpolative procedures.

iii) The Method of Least Squares.

As has been pointed out refinement consists of adjusting atomic parameters so as to minimise some function of the observed and corresponding calculated structure amplitudes. Hughes (1941) first drew attention to the fact that a least squares procedure can be applied to structure refinement.

The function generally minimised is

$$R = \sum w(|F_o|(hkl) - |F_c|(hkl))^2$$
$$= \sum w\Delta^2 \quad \text{----------} \quad (1.9)$$

The summation is operated over all independent terms and w is a weighting factor used since the $|F_o|$ values of all planes cannot be obtained with the same accuracy. Various weighting systems have been developed, all of which attempt to make w inversely proportional to the square of the probable error in $|F_o|$.

Let U_1, U_2, -------, U_n be the n parameters on which $|F_c|$ is dependent. These may be coordinates, thermal parameters or other factors. Then for equation (1.9) to be a minimum:-

$$\frac{\partial \sum w\Delta^2}{\partial U_j} = 0 \quad \text{where } j = 1, 2, \text{------}, n.$$

$$\text{i.e. } \sum w\Delta \frac{\partial \Delta}{\partial U_j} = 0 \quad \text{----------} \quad (1.10).$$

For a set of U_j values, which must approximate to the correct set, the normal equations for the parameter corrections,

ϵ_j, are the n simultaneous linear equations

$$\sum_{i=1} \epsilon_i \left(\sum w \frac{\partial \Delta}{\partial v_j} \frac{\partial \Delta}{\partial v_i} \right) = - \sum w \Delta \frac{\partial \Delta}{\partial v_j} \quad \ldots\ldots \quad (1.11)$$

(for $j = 1, 2, \ldots\ldots, n.$)

where $\frac{\partial \Delta}{\partial v_j}$ etc. are evaluated for the trial set of parameters. The off-diagonal terms such as $\sum w \frac{\partial \Delta}{\partial v_j} \frac{\partial \Delta}{\partial v_i}$ of the corrections in the normal equations can be omitted in the refinement. The atomic and thermal parameters can be treated independently.

In the least squares programme written for DEUCE by Rollett (1961) the normal matrix is computed in three parts:-

1) a three-by-three matrix for the three positional parameters per atom,
2) a six-by-six matrix for the six anisotropic thermal vibrations per atom,
3) a two-by-two matrix in order to yield the overall scale factor.

Another parameter, not adjusted by the programme, is Q which takes account of the overall isotropic vibration factor.

Two principle weighting systems are available in the DEUCE programme.

(1) $\sqrt{w_i}$. If $|F_o| \leq |F^*|$, $\sqrt{w_i} = 1$ and if $|F_o| > |F^*|$ $\sqrt{w_i} = |F^*|/|F_o|$. $|F^*|$ is a constant and can safely be set equal to eight times the minimum $|F_o|$ value.

(2) $\sqrt{w_2}$ If $|F_o| \leq |F^*|$, $\sqrt{w_2} = \frac{|F_o|}{|F^*|}$ and if $|F_o| > |F^*|$, $W_2 = \frac{|F^*|}{|F_o|}$ where $|F^*|$ has the same significance as in (1)

Cochran (1948) showed that the Fourier series method is closely analagous to the least squares procedure. The atomic coordinates obtained from a Fourier map are such as to minimise $\sum \frac{1}{f_r} \Delta^2$ so that the weighting factor for each observation is inversely proportional to the appropriate atomic scattering factor. This obviously places great emphasis on the contributions to the F_o map from high order reflections. Cochran explains that this disadvantage can be surmounted by employing an artificial temperature factor, α, which confers unit weight on all observations.

The outstanding benefits of the least-squares procedure are the absence of series-termination errors and the facility for assigning different weights to individual $|F_o|$ values.

1.(4). Anomalous Dispersion and the Determination of Molecular Absolute Stereochemistry.

The symmetry of centrosymmetrical space groups determines that the reflections from (hkl) and $(\bar{h}\bar{k}\bar{l})$ are indistinguishable. With non-centrosymmetrical crystals also, the intensities, I(hkl) and $I(\bar{h}\bar{k}\bar{l})$ are normally identical.

This is known as Friedel's Law. Under these circumstances it would obviously be impossible to distinguish enantiomorphous pairs of molecules.

In order to determine the absolute stereochemistry of a molecule experimental conditions in which Friedel's Law breaks down would have to be used. This situation can be realised if it is possible to obtain an anomalous phase advance between the incident and scattered beam for at least one atom in the molecule, and this can be attained if this atom has an absorption edge just on the long-wavelength side of the incident beam.

The result of this is that the normal atomic scattering factor has to be corrected by a real and an imaginary part -

$$f = f_0 + \Delta f' + \Delta i f'' \quad \text{---------- (1.12)}$$

These dispersion corrections were first listed for three different incident radiations by Dauben and Templeton (1955) and have been extended and modified to give the factors at various values of $\sin\theta/\lambda$ (International Tables for Crystallography, Volume III, 1962a).

In the structure factor expression it is essential that the terms for normal and anomalous scattering have the correct signs with respect to one another. This means that great care has to be taken in indexing photographs and in assigning axial directions as carefully explained by Peerdeman and Bijvoet (1956).

The method was first used in the analysis of the configuration of the tartrate ion in sodium rubidium tartrate by Bijvoet and his collaborators (1951). They used zirconium K_α radiation (λ = 0.7864) which causes a phase advance at the rubidium ions with a K absorption edge of 0.814Å.

Peterson (1955) later showed that anomalous dispersion effects could be obtained when the absorption edge of the element was at a considerably greater wavelength than that of the incident radiation.

1.(5). Accuracy of X-ray Structure Analysis.

When the final atomic coordinates of a molecular structure have been attained, the normal procedure is to calculate various molecular parameters such as bond lengths and angles using standard trigonometric procedures. The measurements obtained for these parameters will inevitably deviate from the accepted values such as are listed in International Tables for Crystallography, Vol. III (1962b). The problem is to discover whether these differences are small enough to have arisen from experimental error, or whether they are significant. This treatment of necessity has recourse to statistical theory and a full account has been given by Cruickshank and Robertson (1953).

When the block diagonal approximation of the least squares method has been employed, the standard deviations of the parameters U_1, U_2 etc. on which $|F_c|$ is dependent can be found from the expression

$$\sigma(U_j)^2 = \frac{\sum w \Delta^2}{(n-s)\sum w \frac{\partial \Delta}{\partial U_j}\frac{\partial \Delta}{\partial U_j}} \quad \ldots\ldots\ldots (1.13)$$

The standard deviation of a bond length between two atoms is given by the equation

$$\sigma(l) = (\sigma^2(A)+\sigma^2(B))^{\frac{1}{2}} \quad \text{---------} \quad (1.14)$$

where $\sigma(A)$ and $\sigma(B)$ are the standard deviations of the positions of atoms A and B.

The standard deviation of the angle β at B between the bonds AB and BC is given by

$$\sigma^2(\beta) = \frac{\sigma^2(A)}{(AB)^2} + \sigma^2(B)\left(\frac{1}{(AB)^2} - \frac{2\cos\beta}{(AB)(BC)} + \frac{1}{(BC)^2}\right) + \frac{\sigma^2(C)}{(BC)^2}$$

----------(1.15)

The significance of the standard deviation is that errors of a magnitude greater than 3σ are expected to occur only with a frequency of 1 in 1000. 3σ is often called the maximum possible error and if an observation is outwith this limit the deviation can be said to be significant.

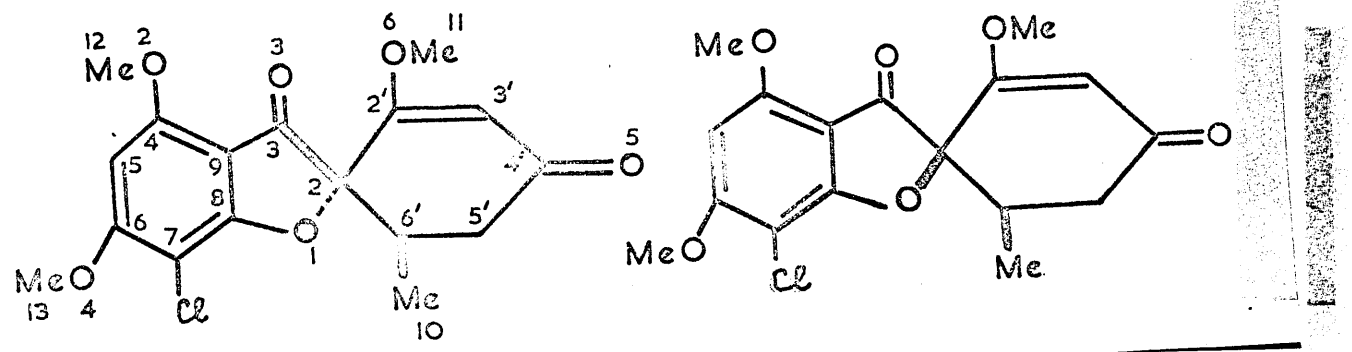
PART II

THE STEREOCHEMISTRY OF GRISEOFULVIN: X-RAY ANALYSIS OF 5-BROMOGRISEOFULVIN.

2.(1). Introduction.

Griseofulvin is a neutral antifungal antibiotic which has found wide application in the treatment of diseases of the skin and hair of both men and animals.

The compound was first isolated by Raistrick and his collaborators (1939) from the mycelium of Penicillium griseofulvum and has subsequently been synthesised in four different ways. The constitution of the molecule was established by the research group of Grove and MacMillan at Imperial Chemical Industries' Akers Laboratories (1952), using conventional degradative and spectroscopic methods. These results led to the proposal of one or other of the following configurations for griseofulvin (with the numbering system indicated in one of them).



I II

Grove and his co-workers (1952) established the absolute configuration of position 6' by using oxidative degradation

with periodate and extracting (+)- methylsuccinic acid which has been related to D-glyceraldehyde.

The only distinguishing feature between I and II is the configuration at the spiran centre, 2, viz. are Me(10) and the carbonyl group C(3) = O(3) cis - or trans - related, respectively? MacMillan (1959) attempted to answer this problem by treating griseofulvin with alkali and examining the equilibrium mixture of the two diastereoisomers, (I and II), since the ring defined by C(3), C(9), C(8), O(1), C(2) opens and recyclises in the process by the scission of bond C(2)-C(3). He found that he obtained 40% of griseofulvin and 60% of the epimer. Consideration of steric effects led to the conclusion that the less favoured configuration would be the one in which the bulky O(3) atom and Me(10) group were cis to one another. MacMillan concluded that griseofulvin must be the less sterically favourable isomer since he obtained it in only 40% yield from the equilibrium mixture. The total configuration of griseofulvin was thus shown to be as I, and epi-griseofulvin as II.

While this represents an attractive chemical solution to the problem, it has the inherent weakness that the ratio of the epimers obtained on treatment with alkali is rather close to unity to be taken as very conclusive. It was to

settle this problem emphatically that this x-ray analysis was undertaken.

The question arose as to whether or not chlorine could be used as an effective phase determining heavy atom. Calculation showed that the value of r (section 1.(2)) is 0.53 which is rather too low and would lead to a fairly large average phase angle error in a non-centrosymmetrical space group. It was apparent that another atom of high atomic number would have to be incorporated in the structure if the heavy atom method was going to be pursued.

A very satisfactory method of accomplishing this is to attempt to recrystallise the material from a solvent the molecules of which contain a heavy atom, in the hope of forming solvates. This procedure is a good one; firstly, because there is no interference with the chemical structure of the molecule under consideration, and secondly, because the experimental skill and time required are kept at a minimum.

Griseofulvin was recrystallised from the solvents methylene bromide and methylene chloride. In both cases good crystals were obtained which were found to contain equimolar proportions of griseofulvin and solvent. Unit cell data for the methylene bromide solvate crystals were determined as follows:-

a 11.14Å b 8.71Å c 11.81Å

$\beta = 115^{\circ}42'$.

The crystals are of the monoclinic system and the only systematic absences occur along the (oko) axis when k is odd. This indicates a choice of space groups $P2_1$ or $P2_1/m$. The latter is ruled out as the molecule is optically active and thus cannot crystallise in a centrosymmetric space group.

When an attempt was made to start collecting upper layer data it was noticed that the crystal was decomposing and it was found to be losing the included solvent. It was then discovered that the methylene chloride solvate was also unstable. In order to overcome this problem a crystal was sealed in a capillary tube with a small quantity of the mother liquour, but in this case the scattering from the solvent molecules was so intense that the project had to be abandoned.

It should be remarked that Cheung and Sim (1964) have successfully used the above method in their analysis of aflatoxin G_1. Using the isomorphous substitution method of phase-determination, they have been able to solve the structures of the crystals containing bromobenzene, bromothiophene and benzene. It was not found necessary to encapsulate the material.

At this stage we were provided with crystals of 5-bromogriseofulvin by Dr. T. Walker of Glaxo Laboratories Limited. This molecule contains two heavy atoms viz.

chlorine and bromine and the corresponding value of r is 1.22. This indicated that there would be a fair chance of a low average phase angle error and that the situation was suitable for application of the heavy atom method.

2.(2). Experimental.

Rotation, oscillation, Weissenberg and precession photographs were taken with copper - K_α ($\lambda = 1.5418\text{Å}$) and molybdenum - K_α ($\lambda = 0.7107\text{Å}$) radiations. Rotation and precession photographs were used for the unit cell parameters. A small crystal completely bathed in a uniform x-ray beam was used for the recording of intensities. No absorption corrections were applied. The intensities were collected on zero layer and equi-inclination upper layer Weissenberg photographs obtained by rotating the crystal about the unique b-axis, the reciprocal lattice nets hol,------, h5l being registered in this way. Further intensity data were gathered from hko and okl precession photographs. The estimation of intensities was performed visually using a calibrated step-wedge. All Weissenberg data were collected using the multiple-film technique of Robertson (1943), and the intensities on successive films of upper-layer series were put on the same scale by means of a variable film factor due to Rossmann (1956).

Precession data were collected by means of a series of timed exposures followed by simultaneous developing. Values for the structure amplitudes were obtained from the intensity data by means of the usual mosaic-block crystal formulae first worked out by Darwin (1914).

The various zones of $|F_o|$ values were placed on the same relative scale by comparison of common reflections, although, at a later stage in the analysis they were correlated with the $|F_c|$ values and thus were put on an absolute scale. In all 1156 independent structure amplitudes were obtained, of which 27 were less than the least observable value.

The density of the crystals was obtained by standard pyknometric methods using aqueous potassium iodide solutions.

2.(3). Crystal Data.

$C_{17}H_{16}BrClO_6$ $M = 431.7$

Monoclinic $a = 10.96 \pm 0.02$Å

$b = 8.61 \pm 0.01$Å

$c = 10.27 \pm 0.06$Å

$\beta = 108°30'$

Volume of unit cell = 919Å^3

For Z = 2, D(calculated) = 1.56 gm./cc.

D(observed) = 1.54 gm./cc.

F(000) = 436

Linear absorption coefficient for x-rays ($\lambda = 1.542\text{Å}$)
$\mu = 49.6$ cm.$^{-1}$.

Systematically absent spectra: (oko) when $k = 2n+1$

This indicates space group $P2_1$ or $P2_1/m$.

As the molecule is optically active it cannot possess a mirror plane or centre of symmetry, and so $P2_1$ is the correct space group.

2.(4). Location of the Heavy Atom Positions.

For a crystal belonging to the monoclinic system with a unique b axis the Patterson function expression, P(uvw), is given by

$$P(uvw) = \frac{4}{V_c} \sum_{o}^{\infty} \sum_{o}^{\infty} \sum_{o}^{\infty} (|F(hkl)|^2 \cos 2\pi(hu+lw) + |F(\bar{h}kl)|^2 \cos 2\pi(hu-lw)) \cos 2\pi kv.$$

which can be simply reduced to two-dimensional projection expressions.

The first projection to be studied was (010). The symmetry of this map is p2, so that it is only necessary to compute the function over half the unit cell area. In this case it was evaluated from u = 0 to u = 1 and from w = 0 to $w = \frac{1}{2}$. The contoured map is shown in Fig. 1.

Four prominent peaks should appear on this map, since the bromine and chlorine atomic coordinates are (x_{Br}, z_{Br}),

$(\bar{x}_{Br}, \bar{z}_{Br})$ and (x_{Cl}, z_{Cl}), $(\bar{x}_{Cl}, \bar{z}_{Cl})$ respectively. These Patterson peaks are:- (a)$(2x_{Br}, 2z_{Br})$, (b)$(2x_{Cl}, 2z_{Cl})$, (c)$(x_{Br} + x_{Cl}, z_{Br} + z_{Cl})$ and (d)$(x_{Br} - x_{Cl}, z_{Br} - z_{Cl})$.

The bromine-bromine vector, the highest peak present, showed up clearly and is marked A on the map, but this was the only peak which could be identified with any certainty.

The fractional coordinates obtained for bromine in this way were

$x/a = 0.2567$ $\qquad$ $z/c = 0.1054$

In order to ascertain the x- and z-coordinates of the chlorine atom it was decided to run a set of hol structure factors phased only on the bromine atoms and use these as coefficients in a two-dimensional Fourier synthesis.

The symmetry of this projection is p2, so that it is again only necessary to evaluate the electron density over half the unit cell area. The computation was performed from $x = 0$ to $x = 1$ and from $z = 0$ to $z = \frac{1}{2}$. The resulting distribution is shown in Fig. 2.

The bromine atom showed up in the expected position, B, and, although the resolution of the chlorine atom was rather badly defined due to coalescence with the bromine atom, it clearly had to be placed at K.

The coordinates evaluated from this map are

$x/a = 0.2541$ $\qquad$ $z/c = 0.1030$ for bromine

and $x/a = 0.2689$ $\qquad$ $z/c = 0.1875$ for chlorine.

Reverting to the hol Patterson map again it was found possible to assign peak (c) to site C and peak (d) was discovered to be merged with the origin vector at D. Vector (b), however, did not come up as a maximum on the map. Its situation is indicated by E.

In the space group $P2_1$ the choice of origin along the screw axis is arbitrary and it is convenient to place it midway between the bromine atom whose coordinates are given above and the symmetrically related one. This means that the y-fractional coordinate for bromine is $\frac{1}{4}$.

The (001) Patterson projection was computed with a view to establishing the y-coordinate of the chlorine atom. The symmetry of this map is pmm, so that the calculation was only performed over one quarter of the unit cell area, viz. from u = 0 to u = $\frac{1}{2}$ and from v = 0 to v = $\frac{1}{2}$. Since the x-coordinates of the two halogen atoms had already been determined, it was only necessary to search for peaks along certain lines of constant u-values. The map is shown in Fig. 3.

The coordinates of the two bromine and two chlorine atoms respectively are

(x_{Br}, y_{Br}), $(\bar{x}_{Br}, \frac{1}{2} + y_{Br})$, and (x_{Cl}, y_{Cl}), $(\bar{x}_{Cl}, \frac{1}{2} + y_{Cl})$.

Among the expected vectors between these atoms are

(a)$(2x_{Br}, \frac{1}{2})$, (b)$(2x_{Cl}, \frac{1}{2})$, (c)$(x_{Cl} - x_{Br}, \frac{1}{2} + y_{Cl} + y_{Br})$

(d)$(x_{Cl} + x_{Br}, y_{Cl} - \frac{1}{2} - y_{Br})$.

Peaks (a) and (b) show up, as expected, on the line at $v = \frac{1}{2}$, although they are not resolved. They are marked F and G respectively.

In order to ascertain the chlorine y-coordinate, a search for maxima need only be made along the lines at $u = x_{Cl} - x_{Br}$ i.e. 0.0148 and at $u = x_{Cl} + x_{Br}$ i.e. 0.5230 or 0.4770. The vectors (c) and (d) are denoted by H and J on Fig. 3. Both of these lead to values of $\frac{1}{4}$ for y_{Cl}.

The (100) Patterson projection was next calculated. The basic symmetry of this map is the same as the (001) projection and the vectors involved identical except that $\underline{x}$ and $\underline{u}$ are interchanged with $\underline{z}$ and $\underline{w}$. The distribution, which is shown in Fig. 4, confirms the previous findings.

It had been found rather difficult to evaluate accurate x- and z-coordinates for the chlorine atoms from these projections. With this in mind it was decided to compute the Harker section at $v = \frac{1}{2}$. in order to obtain a better estimate of these values. Fig. 5 shows this vector distribution.

The vector between chlorine (x_{Cl}, y_{Cl}, z_{Cl}) and bromine ($\bar{x}_{Br}$, $\frac{1}{2} + y_{Br}$, $\bar{z}_{Br}$) is situated at $u = x_{Cl} + x_{Br}$, $v = y_{Cl} - \frac{1}{2} - y_{Br}$ and $w = z_{Cl} + z_{Br}$. Since the y-coordinates for both halogen atoms are the same, the value of $\underline{v}$ simplifies to $\frac{1}{2}$. This peak showed up well in the Harker section and is marked L. The bromine-bromine vector is marked M.

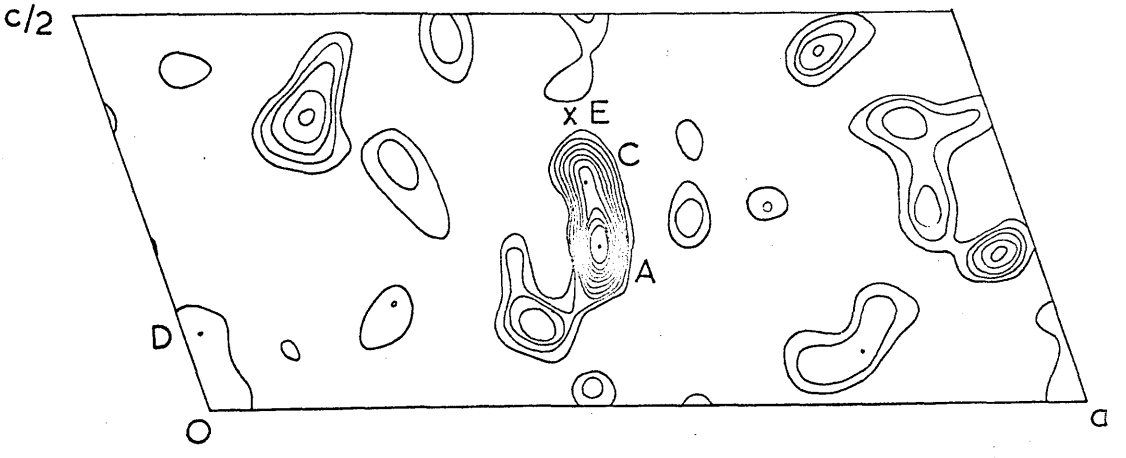


Fig. 1 5-Bromogriseofulvin.

Patterson projection along the b-axis. Contours at arbitrary intervals. Origin peak contours omitted.

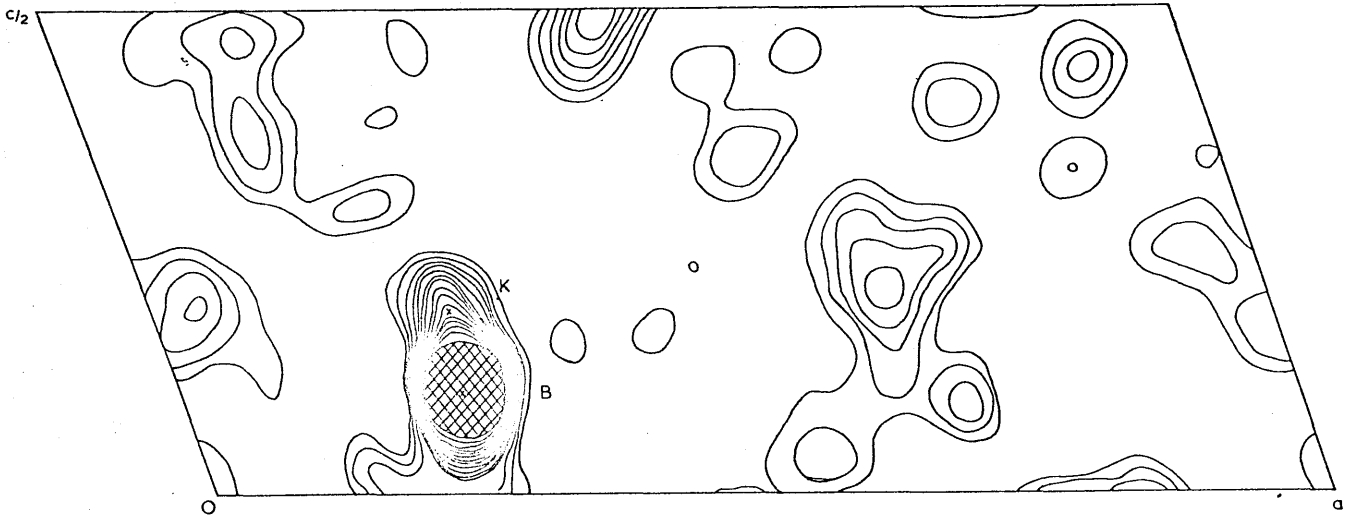


Fig. 2 5-Bromogriseofulvin.

First Fourier projection along the b-axis. Contour scale arbitrary. Higher contours omitted around bromine atom.

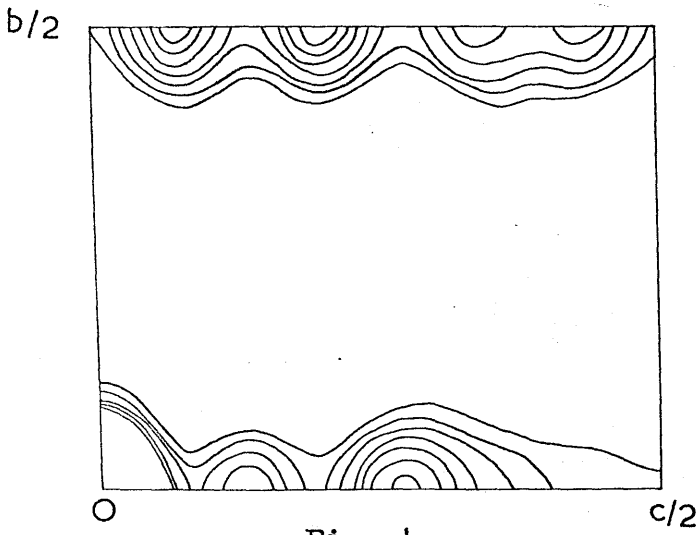


Fig. 4

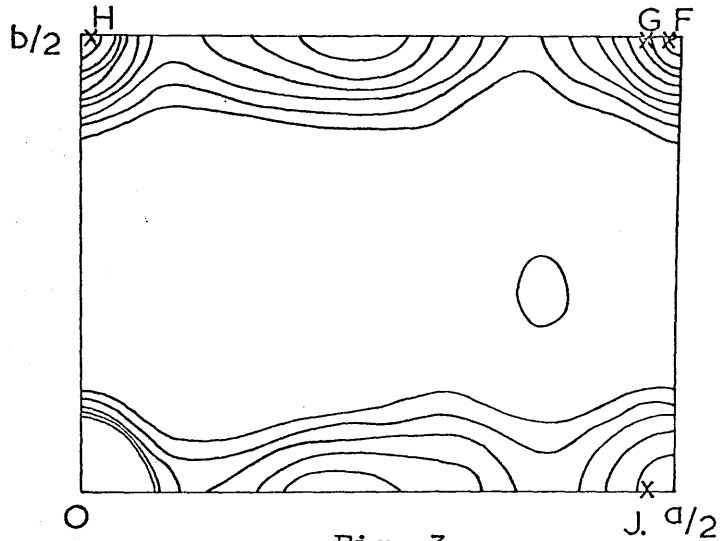


Fig. 3

5-Bromogriseofulvin.

Patterson projections along the c- and a-axes respectively. Contour scale arbitrary. Origin peak contours omitted.

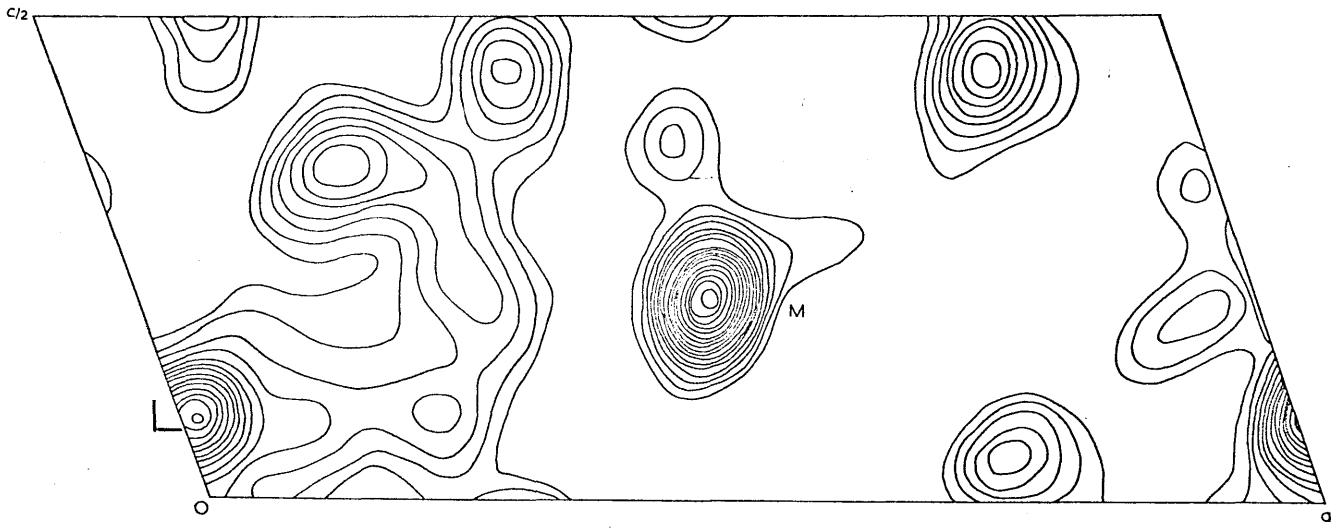


Fig. 5 5-Bromogriseofulvin.

Harker section (u, $\frac{1}{2}$, w). Contours at arbitrary intervals.

The coordinates obtained from this synthesis were

x/a = 0.2546 y/b = 0.2500 z/c = 0.1030 for bromine

x/a = 0.2690 y/b = 0.2500 z/c = 0.1879 for chlorine

2.(5). Pseudo-symmetry in Space Group, $P2_1$.

Associated with space group $P2_1$ is a well-known phasing ambiguity.

In the case of 5-bromogriseofulvin with two molecules per unit cell it is obvious that the two heavy bromine atoms are linked by a centre of symmetry, which, of course, does not operate on the two molecules as a whole.
Assuming that the bromine atoms alone are used in the first structure factor calculation, then the resultant phases will be either 0 or π. This implies that a false centre of symmetry will be forced into the calculated structure, so that in the subsequently evaluated Fourier map peaks will appear not only at true atomic positions, but also at extra points related to the first by the false centre of symmetry. From this it can be seen that the initial phases cannot determine a unique set of atomic sites, but merely limit the position of each atom to one of two alternatives.

In $P2_1$ the coordinates of one of the light atoms in the asymmetric unit can be denoted (i) (xyz) and (ii) $(\bar{x}, \frac{1}{2} + y, \bar{z})$.

The operation of the false centre of symmetry will generate extra positions at (iii) $(\bar{x}\bar{y}\bar{z})$ and (iv) $(x, \frac{1}{2} - y, z)$. Examination of these four locations shows that (i) and (iv) are related by a false mirror plane at $y = \frac{1}{4}$ and $y = \frac{3}{4}$. Positions (ii) and (iii) are similarly pseudosymmetrically linked. The y-parameter of any atom is then either $Y = \frac{1}{4} + y'$ or $Y = \frac{1}{4} - y'$, where y' is the displacement from the false mirror plane in the y-direction.

When atoms situated off the plane at $y = \frac{1}{4}$ have been conclusively selected and their coordinates used in a phasing calculation, the phase angles are free to assume general values so that the centre of symmetry and hence the mirror plane begin to be destroyed. Even after complete structure analysis, however, small 'ghost' mirror image peaks may yet persist. This is due to too large a weight still being assigned to the heavy atom contributions viz. the atomic parameters are still too close to those obtained on the basis of the heavy atom positions alone.

This subject has been discussed in some detail by Carlisle and Crowfoot (1945) in a paper discussing the structure analysis of cholesteryl iodide.

In the case of 5-bromogriseofulvin it was hoped to avoid this problem because of the presence of a second non-symmetrically related phase-determining atom - chlorine.

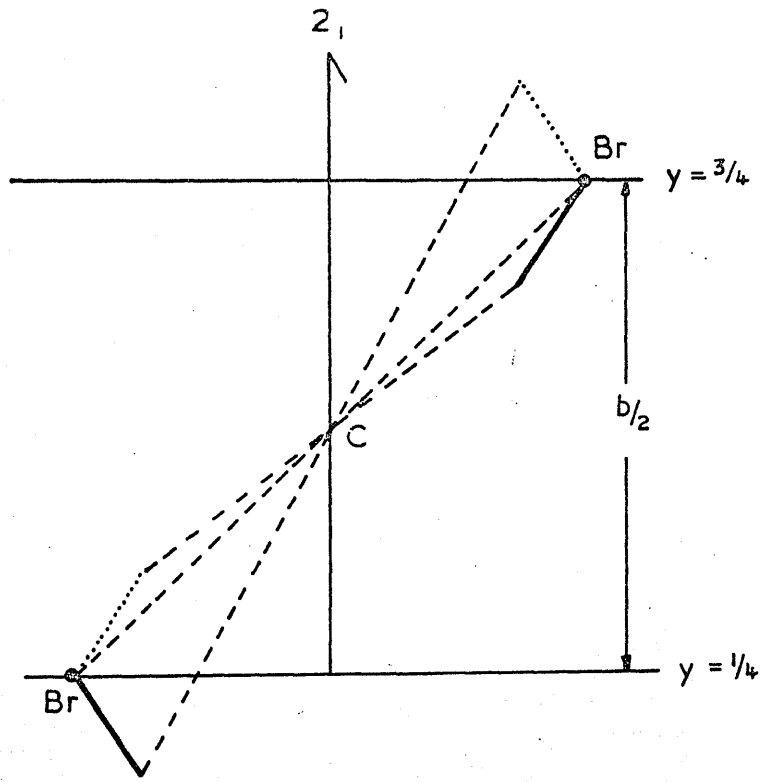


FIG. 6 (a).

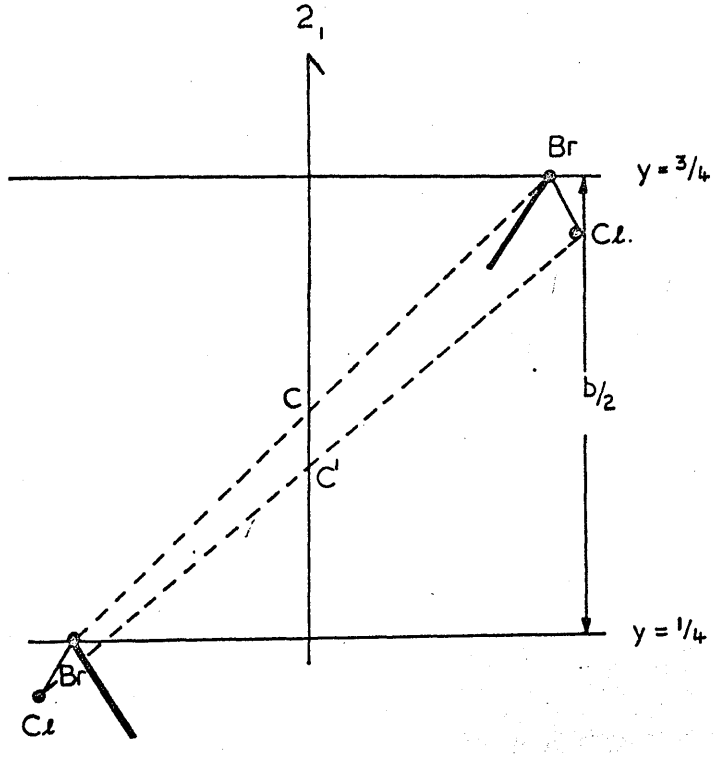


FIG. 6 (b).

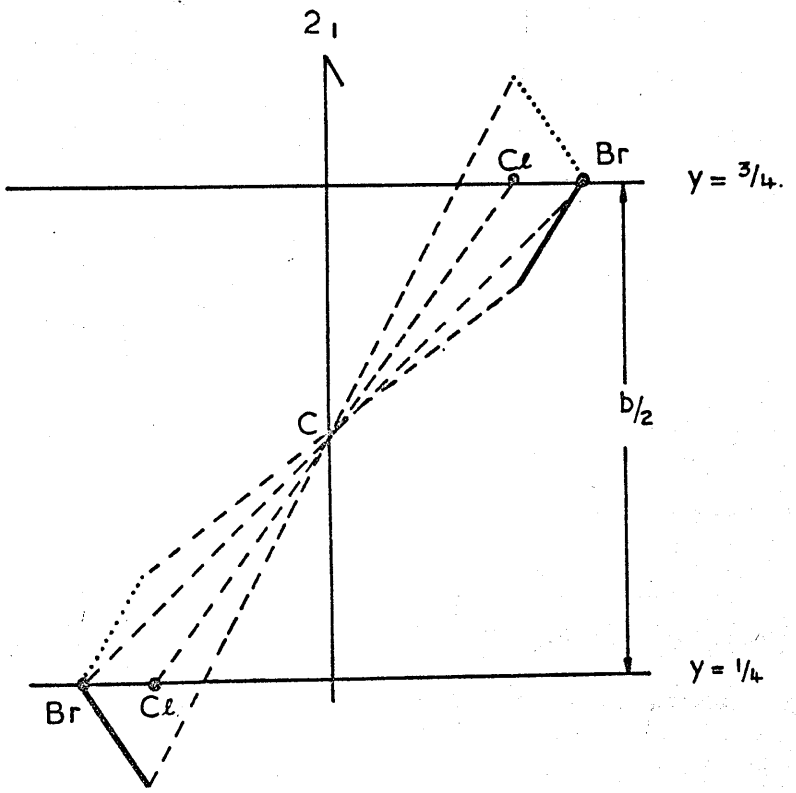


FIG. 6 (c).

The two chlorine atoms are, of course, connected by a centre of symmetry, but it is rather unlikely that this coincides with that linking the bromines. In the event of non-coalescence of these two centres, the overall symmetry will be annulled and no pseudo-symmetric problem arises.

However, as seen in 2.(4), the y-coordinates of both halogen atoms are almost identical. This corresponds, unfortunately, to the rather unlikely situation mentioned earlier in this section where the centres of symmetry linking the bromines and the chlorines are coincident. This being the case, the pseudo-symmetric problem still had to be faced.

The three situations described above are illustrated in Figs. 6(a), (b) and (c) respectively. The short thick line represents the light atom part of the structure; the broken line, the operation of the false centre of symmetry; the dotted line, the mirror image 'ghost' structure and C and C', centres of symmetry.

2.(6). Solution of the Structure.

If the coordinates for bromine and chlorine given at the end of 2.(4) were used for calculating structure factors which were then used as Fourier coefficients in an electron density distribution, there would be mirror planes through this distribution at $y = \frac{1}{4}$ and $y = \frac{3}{4}$. In order to obviate

this to a small extent, the y-coordinate for chlorine was altered to 0.2400.

These coordinates and an assumed isotropic temperature factor for both atoms of $\alpha = 2.75$ (where the temperature factor is given by $2^{-\alpha \sin^2\theta}$) were used in the calculation of a first set of structure factors. The resultant discrepancy, R, measured over all reflections was 42.2%. It was decided to reject structure factors which had an $|F_o|$ value greater than twice the $|F_c|$ value. This ensures that only terms which have been approximately correctly phased by the bromine and chlorine contributions are used as Fourier coefficients. After this elimination process, there were 1,030 terms remaining.

The unit cell was divided into a three-dimensional grid with intervals of a/48, b/30 and c/48. This corresponds to interspaces of 0.23Å, 0.29Å, and 0.25Å respectively parallel to the axial directions, and ensures that the resolution of atoms will be good and that it will be possible to calculate atomic coordinates accurately by interpolative procedures. As there are two equivalent positions, it was only necessary to compute the electron density over half of the unit cell, and that portion chosen was a x b/2 x c.

The electron density was evaluated in sections parallel to (010) for each grid point in the (xz) plane and each map contoured. These contours were then mapped out on glass sheets which were stacked perpendicularly to the b-axis in a frame. This confers a three-dimensional effect to the distribution which can be examined for recognisable structural features.

From the first Fourier map it was immediately obvious that not only did the bromine and chlorine atoms lie on the mirror plane, but the benzene ring atoms and their immediate substituents as well as atoms O(3), O(5) and C(2) all had y-coordinates of approximately $\frac{1}{4}$. The other atoms which lay off this plane were present with their complementary mirror images, but no choice between them could be made at this stage.

The coordinates of the nine better-defined atoms (including those of bromine and chlorine) were calculated by a method of interpolation in the figure field due to Booth (1948), the factors being conveniently listed in tabular form. The equation of the mean plane through these nine atoms -Br, Cl, O(4), O(2), O(3), O(5), C(2), C(4) and C(6) - was evaluated in the form

$$y = 0.01724x + 0.02626z + 0.20044 \text{ ----------} (2.1).$$

An accurate scale drawing, based on standard valency bond lengths and angles, was now made of the benzene and five-membered rings part of the structure, and the x- and z-coordinates of atoms C(3), C(5), C(7), C(8), C(9) and O(1) were read off. The y-coordinates of each of these six atoms were found in turn by substituting their x- and z- values in equation (2.1). Thus the coordinates of fifteen atoms were now obtained.

The largest deviation from the false mirror plane by any of these atoms is only 0.137Å. This means that the phases deduced from their contributions will still be close to 0 or π, so that the pseudo-symmetry will be largely retained. It was encouraging, however, to note that this maximum displacement was of the chlorine atom which had been placed only 0.087Å off the plane.

The second structure factor calculation was evaluated on the basis of the above fifteen sets of atomic coordinates using the same uniform isotropic temperature factor, $\alpha = 2.75$. The overall R-value was 35.7% - a drop of 6.5% i.e. about 0.5% per extra atom. Of these structure factors, 1062 were included in the next Fourier synthesis.

From this map it was found possible to determine the coordinates of seven further atoms. C(4'), lying close to the mirror plane, was readily defined. The cyclohexene

ring lies approximately perpendicularly to the remainder of the cyclic system, and atoms C(2), C(4') and O(5) are coplanar with the benzene ring. This results in C(2') and C(6') having approximately the same x- and z-coordinates and y-coordinates equidistantly placed on either side of the pseudo-mirror plane. Even although this is a rough approximation (no account has been taken of the fact that bond C(2') - C(3') is 4.5% shorter than bond C(6') - C(5')) it was reckoned that atom C(2') would coincide with the 'ghost' peak from C(6') and vice versa. A similar argument holds for C(3') and C(5'). This will undoubtedly lead to some deviation from the true atomic positions, but, nevertheless, the four distinct maxima were calculated. Atom C(10) was not at all clearly resolved, but C(11), C(12), C(13) and O(6) along with their mirror images were unmistakably defined. In order to ascertain if any of these could be distinguished from its 'ghost' a comparison of relative peak heights was made.

Atom	ρ above mirror plane	ρ below mirror plane
C(11)	1.35	1.27
C(12)	1.31	1.31
C(13)	1.42	1.43
O(6)	2.28	2.17

From these results it was decided that C(11) and O(6) could safely be inserted above the plane, but that a decision as to C(12) and C(13) would have to be postponed.

The maxima of all twenty-two atoms were now calculated by Booth's method and it was noted that the chlorine atom was now 0.172Å away from the mirror plane in the y-direction. This, along with the fact that atoms C(11) and O(6) have been inserted well off the plane, should further reduce the false symmetry in the next Fourier calculation.

The next phasing calculation was carried out using the twenty-two sets of atomic coordinates and the same uniform isotropic temperature factor. The discrepancy, summed over all the terms was 30.2% - a decrease of 5.5%. The structure factors of 1,109 reflections were employed as coefficients in the next cycle of Fourier calculations.

In the third electron density map the pseudo-symmetry was noticeably reduced and on the basis of peak heights it was possible to locate atoms C(12) and C(13) unambiguously. The only atom still to be placed was the all-important C(10), the relationship of which to bond C(3) = O(3) was the whole point of this analysis. Many of the atoms in the structure were now deviating significantly from the plane at $y = \frac{1}{2}$, the chlorine atom displacement being 0.198Å. The x- and z-coordinates of C(5') were observed to have altered quite

dramatically. This was an expected alteration since the double bond C(2') - C(3') has the effect of distorting the six-membered ring.

The coordinates of the twenty-four atoms so far located were calculated from the figure field and used along with the same uniform α-value in the computation of a fourth set of structure factors, for which the discrepancy was 26.3% - a reduction of 3.9%. 1097 of these terms were included in the subsequent Fourier summation.

The false symmetry in this map was now very much less evident and the true site of C(10) was unambiguously settled. It turned out to be cis - related to the carbonyl group, so that the constitution and stereochemistry of griseofulvin are as portrayed in formula I in section 2.(1).

The coordinates of all twenty-five atoms were calculated from this map by Booth's method and then used along with the previous α-value in a fifth set of structure factors. The overall value for R was 24.3% - a drop of 2.0%.

This completed the structure elucidation and the course of the analysis is indicated in Table 1.

2.(7). Refinement of the Structural Parameters.

The contributions by hydrogen atoms to the structure factors were not taken into account at any stage in the refinement.

1106 of the above structure factors were used in a cycle of F_o synthesis refinement, but the drop in the R-factor - from 24.3% to 24.0% - was so insignificant, that it was decided that this method of refinement would be unrewarding.

It was resolved to attempt to apply the back-shift correction method due to Booth (1946) as mentioned in section 1.(3). Using 1120 of the last set of structure factors F_o and F_c maps were computed and shifts were applied to atomic coordinates and adjustments made in the values of temperature factors for the first time. The discrepancy dropped to 22.5% and all the structure factors were included in a further round of F_o and F_c syntheses.

The coordinates and new temperature parameters obtained from these were then employed in a first cycle of differential synthesis refinement. The DEUCE programme, written by Dr. J.G. Sime, adjusts atomic coordinates and isotropic temperature factors.

The temperature factors used to modify the scattering factors in this programme are of the form $e^{-B_\theta \sin^2\theta/\lambda^2}$ so that it was necessary, first of all, to convert from α-values to B_θ values. This is very simply done by multiplying by 1.648 when the incident radiation is copper K_α.

After four cycles of differential synthesis the value of R had dropped to 20.1% - a decrease of approximately 0.6% per round.

An examination was made between $\sum|F_o|$ and $\sum|F_c|$ for each of the zones - hol, h11,------, h51 - from which data had been collected. The scaling factors increased regularly from 0.9137 for hol to 1.1590 for h51. This suggested that values for $|F_c|$ were being calculated too small for the lower order zones and too large for the higher order zones, and indicated that the atoms were not vibrating isotropically. This implied that anisotropic temperature factors would have to be used and refinement was continued using the least squares programme written by Dr. J.S. Rollett (1961).

After several cycles of least squares using half-shifts and weighting system w_1 (see 1.(3).) with an $|F^*|$ value of 31, the discrepancy had dropped to 16.4% and $\sum w\Delta^2$ had fallen from 24.9 to 16.5. No appreciable decrease in either of these parameters was obtained from the next refinement calculation, and it was decided to apply weighting system w_2.

After two cycles of this refinement it was decided that no further improvement of the atomic parameters could be obtained and the final value for the discrepancy, summed over all the observed terms was 14.0%.

In all the structure factor calculations the theoretical scattering factors used were those of Berghius et al. (1955) for carbon and oxygen, those of Tomiic and Stam (1958) for chlorine and the Thomas-Fermi values (1935) for bromine.

2.(8). Results.

The final atomic coordinates for one molecule are listed in Table 2. The corresponding intramolecular bonded and non-bonded distances are given in Table 3. Table 4 shows the list of intermolecular distances less than 4Å. The final valency bond angles are set out in Table 5.

The standard deviations of atomic coordinates were calculated from the least squares residuals as explained in section 1.(5). and are listed in Table 6. From these results it can be shown that the average estimated standard deviation (e.s.d.) of the bond distance between two light atoms (carbon or oxygen) is about 0.05Å, while that for a valency angle is of the order of 3°.

Table 7 shows the final parameters which define the anisotropic thermal vibrations. They are the individual values of b_{ij} in the equation

$$\exp.\ (-B\sin^2\theta/\lambda^2) = 2^{-(b_{11}h^2+b_{22}k^2+b_{33}l^2+b_{12}hk+b_{23}kl+b_{13}hl)}$$

The values of $|F_o|$, $|F_c|$ and α obtained from the final least squares cycle are shown for all the observed reflections in Table 8.

Using these values for coefficients in a Fourier series, a final three dimensional electron density distribution was calculated. This distribution over one molecule is portrayed in Fig. 7 by means of superimposed contour

sections drawn parallel to (010). The molecular arrangement corresponding to this diagram is shown in Fig. 8.

The packing of the molecules in the crystal as viewed down the b-axis is illustrated in Fig. 9.

In the application of the heavy atom method to a non-centrosymmetrical crystal structure, the final electron density distribution is, to some extent, dependent on the choice of coordinates for lighter atoms which make significant contributions to the structure factors. This point is stressed by Hodgkin et al. (1959) who show, in their analysis of vitamin B_{12} hexacarboxylic acid, that carbon atoms slightly misplaced, even in the presence of a cobalt atom, appear as low elongated peaks in the Fourier map.

The electron density projection down the unique axis, however, in space group $P2_1$ is centrosymmetric so that the accuracy with which the coordinates of the lighter atoms can be assigned is not such an important criterion as in the non-centrosymmetrical case. In this projection the signs of the structure factors are overwhelmingly determined by the presence of the bromine and chlorine atoms. In Fig. 10 the final x- and z-coordinates are shown superimposed on the hol electron density map which was evaluated using structure factors from the last cycle of least squares.

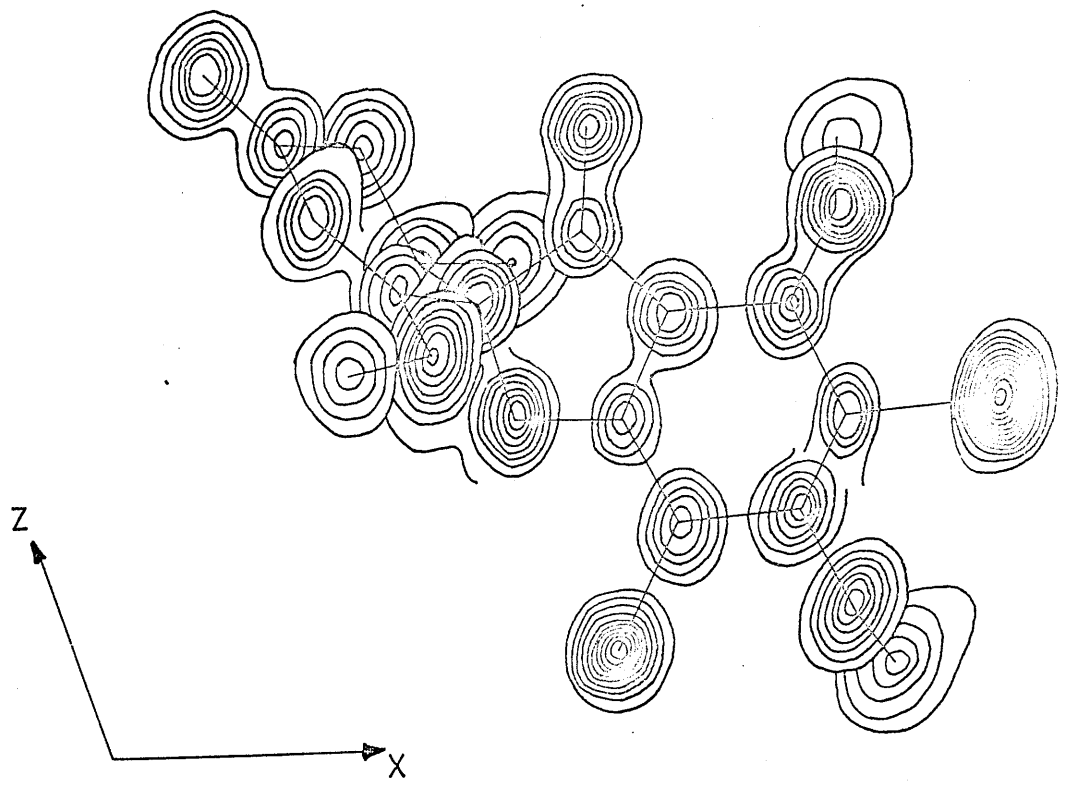


Fig. 7 5-Bromogriseofulvin.

Final superimposed contour section electron-density map drawn parallel to (010). Contour interval 1e/Å^3 except for chlorine (= 2e/Å^3) and bromine (= 3e/Å^3).

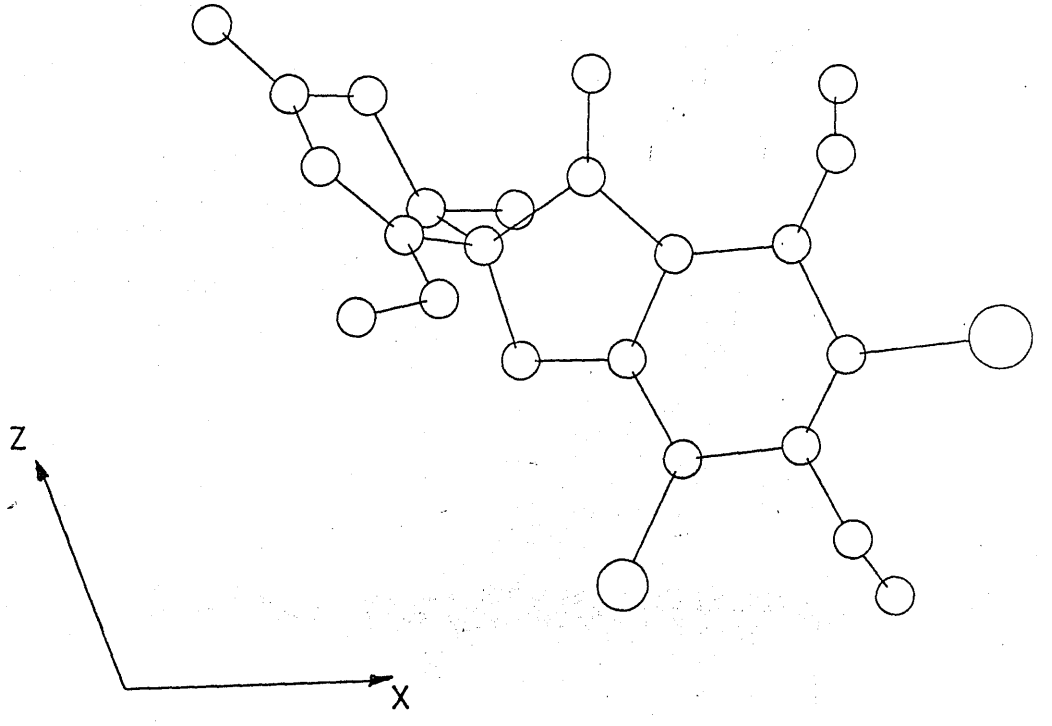


Fig. 8 5-Bromogriseofulvin.

Atomic arrangement corresponding to Fig. 7.

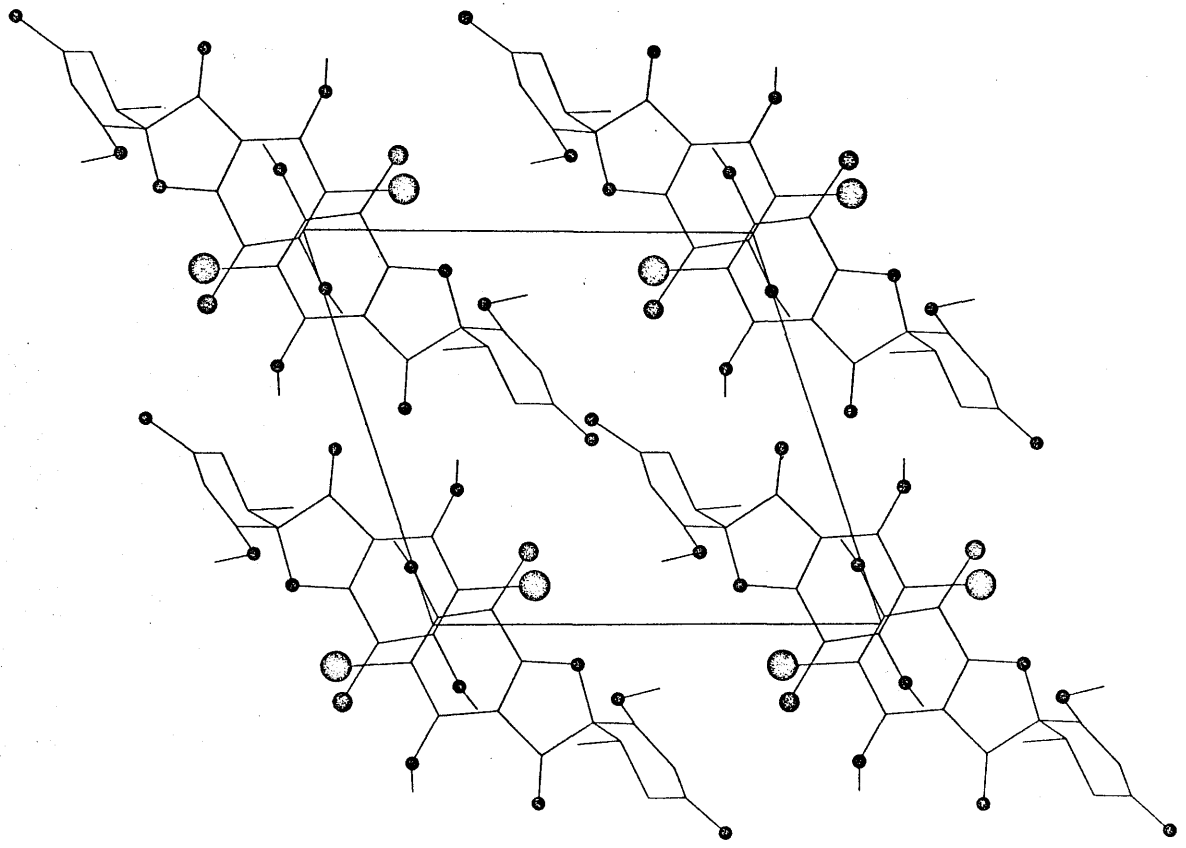


Fig. 9 5-Bromogriseofulvin.

The packing of molecules in the crystal as viewed down the b-axis. The circles in decreasing size represent bromine, chlorine and oxygen atoms respectively.

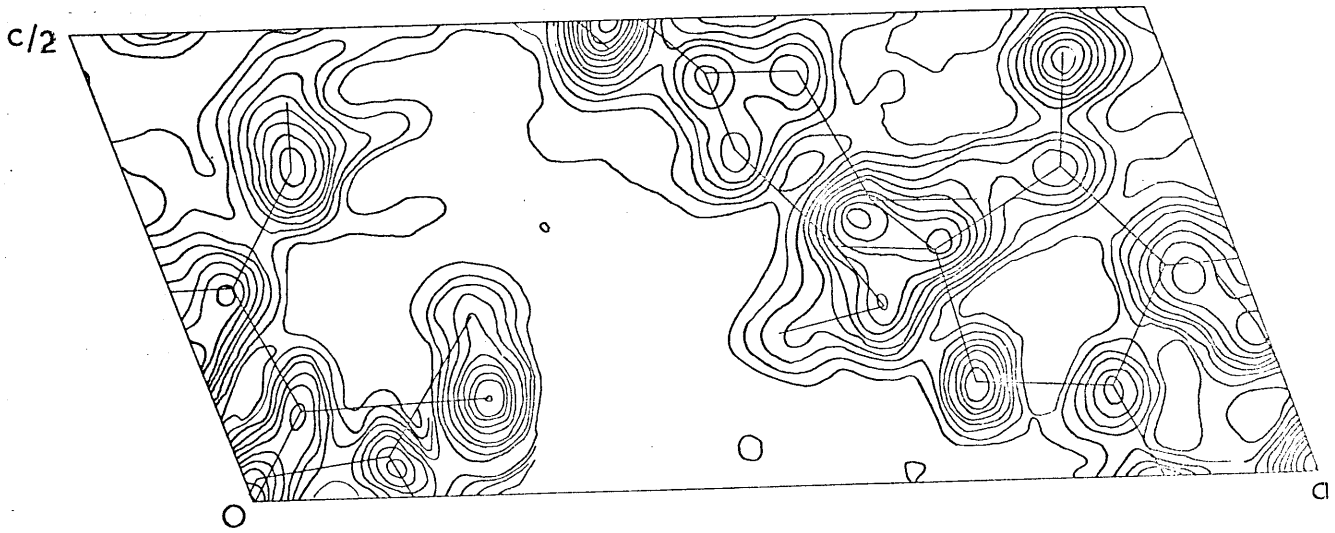


Fig. 10 5-Bromogriseofulvin.

Final Fourier projection on (010) with superimposed molecular skeleton. Contour interval is 5e/Å^3 for bromine and chlorine and 1e/Å^3 for other atoms.

The atomic sites coincide, to a large extent, with peak maxima. It will be noted that this map is quite similar to Fig. 2.

2.(9). Discussion.

As already stated the constitution and stereochemistry of griseofulvin are as in formula I (see section 2.(1).) and confirm the tentative findings of MacMillan (1959). Since the x-ray analysis results have been published, Arison et al. (1963) have come to the same conclusion about the stereochemistry of griseofulvin from nuclear magnetic resonance studies.

The molecular parameters listed in tables 3, 4 and 5 are not very accurate. This is due to several reasons. The presence of both a bromine and a chlorine atom in the molecule means that absorption effects will be quite high, thus reducing the accuracy of the intensity data. The presence of the two heavy atoms also impedes the refinement of the coordinates of the lighter atoms. This is because the latter make a relatively small contribution to each structure factor.

A less obvious factor influencing the relative inaccuracy of the bond lengths and angles is the persistence to some extent of the pseudo-symmetry throughout the course

of the analysis. Srinivasan (1961) has pointed out that in the situation of a non-centrosymmetric structure with phase-dominating atoms or groups centrosymmetrically related it is faulty to ignore the off-diagonal terms of the normal equations of least squares refinement. He comments that this error is equivalent to an application of least squares procedure to two atoms overlapping in projection. Hence, during the refinement of parameters of an atom, A, in a non-centrosymmetric crystal structure containing heavy atoms linked by a centre of symmetry, the interaction of this atom with another atom, B, cannot be ignored when the pair of atoms are accidentally related by the heavy atoms' centre of symmetry. This situation Srinivasan calls "inverse overlap". The matter has also been discussed by Rae and Maslen (1963). An example of this phenomenon is to be found in the case of bromobruceol (Duffield, Jefferies, Maslen and Rae, 1963) where, with the bromine atom in a special position, the structure was refined by a diagonal approximation least squares procedure to an overall discrepancy of 15.6%. Despite this, sp^3-carbon-sp^3-carbon bond lengths as widely divergent as 1.32Å and 1.76Å were reported.

With this in mind it is not surprising that, since Rollett's block diagonal approximation least squares programme was used, with 5-bromogriseofulvin, some of the bond lengths are quite seriously in error.

The average length of the sp^3-carbon-oxygen single bond is 1.46Å in close agreement with values of 1.46Å for bromogeigerin acetate (Hamilton, McPhail and Sim, 1962), 1.47Å for bromodihydroisophoto-χ-santonic lactone acetate (Asher, 1963) and 1.460Å for hydroxy-L-proline (Donohue and Trueblood, 1952). Using Pauling's (1960) covalent bond radii and electronegativity data the reference value for such a bond is 1.43Å. Experimental distances close to this value have been found e.g. 1.424Å for L-threonine (Shoemaker, Donohue, Schomaker and Corey, 1950). The mean sp^2-carbon-oxygen single bond has a length of 1.37Å which is in accord with the results of 1.36Å for salicylic acid (Cochran, 1953) and 1.36Å for atrovenetin trimethyl ether ferrichloride (Paul, 1962). The average carbon-oxygen double bond length, 1.23Å, agrees with the measurements of 1.22Å for N-chloro-succinimide (Brown, 1961) and 1.222Å for p-benzoquinone (Trotter, 1960).

The average carbon-carbon bond length in the benzene ring, 1.40Å, compares favourably with the accepted distance of 1.397Å for benzene. The average sp^3-carbon-sp^3-carbon single bond length of 1.54Å is in good agreement with the standard value of 1.545Å for diamond. The mean sp^2-carbon-sp^2-carbon bond distance, 1.47Å, is close to the values of 1.477Å in p-benzoquinone (Trotter, 1960) and 1.48Å for

benzoic acid (Sim, Robertson and Goodwin, 1955). The average sp^3-carbon - sp^2-carbon bond has a length of 1.49Å and is in accord with 1.49Å for 2-bromo-α-santonin (Asher, 1963) and 1.50Å for bromogeigerin acetate (Hamilton, McPhail and Sim, 1962).

The aromatic carbon-chlorine bond length, 1.69Å is significantly shorter than that of 1.736Å for 4,4' - dichloro-diphenyl sulphone (Sime and Abrahams, 1960) and 1.753Å for 2-chloro-5-nitrobenzoic acid (Ferguson and Sim, 1962,b). A value of 1.711Å, however, has been quoted for 1:3:5-trichlorobenzene (Milledge and Pant, 1960).

The aromatic carbon-bromine bond has a length of 1.91Å which is in good agreement with the measurements of 1.885Å in o-bromobenzoic acid (Ferguson and Sim, 1962,b) and 1.896Å in β - 1:2 - 4:5 - tetrabromobenzene (Gafner and Herbstein, 1960).

None of the intermolecular contacts (Table 4) are significantly shorter than the sum of the Van der Waals' radii of the atoms involved.

In the five-membered ring system O(1), C(2), C(3), C(9), C(8) the average internal valency bond angle is 108°. Frequently the average valency bond angle in five-membered rings is less than 108°. In clerodin bromolactone the value is 106° (Paul, Sim, Hamor and Robertson, 1962), in

isoclovene hydrochloride it is 105° (Clunie and Robertson, 1961) which is also the measurement from himbacine hydrobromide (Fridrichsons and Mathieson, 1962). These values, all of which are considerably smaller than that for 5-bromogriseofulvin, indicate that the ring systems are non-planar with consequent bond angle deformation as was demonstrated in the case of cyclopentane (Pitzer and Donath, 1959).

If the five-membered ring is fused to a benzene ring or includes a double bond, it would be expected that the non-planarity would not be so pronounced and that the average valency bond angle would be rather closer to 108° - the value for a planar five-membered ring - than the examples quoted above. A possible verification of this hypothesis is to be found in the analysis of echitamine bromide (Hamilton, Hamor, Robertson and Sim, 1962) in which there are two five-membered rings only one of which is fused to a benzene ring. The average bond angle in this ring is 107° and in the other case is 104°.

The effect of the double bond in a five membered ring can be illustrated from the case of bromogeigerin acetate (Hamilton, McPhail and Sim, 1962). In the ring including a double bond the angle is 107° and in the other ring without a double bond it is 105°.

The average bond angle in the five-membered ring fused to the benzene ring in macusine-A iodide (McPhail, Robertson, and Sim, 1963) is 108° - identical with the value for 5-bromogriseofulvin.

The equation of the mean plane through the twelve atoms of the hexasubstituted benzene ring was calculated using the method of Schomaker et al. (1959). The equation of the plane is

$$0.0936x - 0.9950y - 0.1703z + 2.0575 = 0$$

Table 9 shows the deviations of these atoms and also of O(3), C(2), C(4') and O(5) from the aromatic plane. If these values are compared with the e.s.d's. of atomic coordinates listed in Table 6, very few of the displacements can be taken as significant. Nevertheless, examination of the deviations of the six atoms directly bonded to the benzene ring shows a suggestion that alternate atoms are above and below the plane of the ring: bromine, C(3) and chlorine lie below the plane and O(2) and O(1) above it. O(4), on the other hand, to conform to this pattern should lie above the plane, but, in fact, is below it. Not much significance can be attached to this postulate, but the results are in broad agreement with those of Ferguson and Sim (1961; 1962,a, b) for ortho-disubstituted benzenes.

The deviation from the mean plane of 0.41Å for O(3) is highly significant, and is probably accounted for by some steric interaction with O(2). Were it not for the fact that C(2) was firmly held by the ring system, this interaction could be relieved by rotation of the group C(9), C(3), O(3), C(2) about the C(3) - C(9) bond. As it is, the strain is diminished by the C(3) - C(9) bond bending out of the plane. This satisfactorily accounts for the fact that of the six direct benzene ring substituents, C(3) is displaced furthest from the plane.

TABLE I

5-Bromogriseofulvin

Course of the Structure Analysis

Operation	Atoms included	R(%)
2D Patterson syntheses	-	-
Harker section at w = $\frac{1}{2}$	-	-
1st 2D hol Fourier synthesis	Br	53.1
2nd 2D hol Fourier synthesis	Br + Cl	46.2
1st 3D Fourier synthesis	Br + Cl	42.2
2nd 3D Fourier synthesis	Br+Cl+8(C)+5(O)	35.7
3rd 3D Fourier synthesis	Br+Cl+14(C)+6(O)	30.2
4th 3D Fourier synthesis	Br+Cl+16(C)+6(O)	26.3
5th 3D Fourier synthesis	Br+Cl+17(C)+6(O)	24.3

TABLE 2

Atomic Coordinates

(Origin of coordinates on two-fold screw axis.)

Atom	x/a	y/b	z/c
C(2)	-0.2798	0.1978	0.2451
C(3)	-0.1367	0.2235	0.3291
C(4)	0.0597	0.2181	0.2251
C(5)	0.0778	0.2504	0.0924
C(6)	-0.0114	0.2441	-0.0213
C(7)	-0.1414	0.2140	-0.0412
C(2')	-0.3703	0.3140	0.2523
C(3')	-0.4283	0.3346	0.3571
C(4')	-0.4312	0.2026	0.4402
C(5')	-0.3450	0.0672	0.4380
C(6')	-0.3296	0.0577	0.2932
C(8)	-0.1657	0.2063	0.0926
C(9)	-0.0731	0.2132	0.2194
C(10)	-0.2257	-0.0758	0.2991
C(11)	-0.4552	0.5720	0.1612
C(12)	0.1780	0.0877	0.4221
C(13)	0.0287	0.1170	-0.2148
O(1)	-0.2883	0.1890	0.1028
O(2)	0.1525	0.2232	0.3458

TABLE 2 (Contd.)

Atom	x/a	y/b	z/c
O(3)	-0.0934	0.2416	0.4505
O(4)	0.0069	0.2596	-0.1540
O(5)	-0.4921	0.1951	0.5249
O(6)	-0.3491	0.4381	0.1852
Cl	-0.2665	0.2277	-0.1888
Br	0.2545	0.2648	0.1018

TABLE 3

Intramolecular bonded distances (Å)

C(2) - C(3)	1.55	O(4) - C(13)	1.43
C(3) - C(9)	1.50	C(7) - Cl	1.69
C(4) - C(9)	1.44	C(3) - O(3)	1.19
C(4) - C(5)	1.46	C(2) - C(2')	1.43
C(5) - C(6)	1.26	C(2') - C(3')	1.42
C(6) - C(7)	1.40	C(3') - C(4')	1.43
C(7) - C(8)	1.48	C(4') - C(5')	1.51
C(8) - C(9)	1.38	C(5') - C(6')	1.55
C(8) - O(1)	1.39	C(6') - C(2)	1.47
C(2) - O(1)	1.44	C(2') - O(6)	1.33
C(4) - O(2)	1.33	O(6) - C(11)	1.60
O(2) - C(12)	1.38	C(4') - O(5)	1.26
C(5) - Br	1.91	C(6') - C(10)	1.61
C(6) - O(4)	1.45		

Intramolecular non-bonded distances (Å)

C(2) ... C(4')	2.98	C(13) ... Br	3.63
C(2) ... C(11)	3.71	C(13) ... Cl	3.46
C(3) ... C(4')	3.75	C(10) ... O(3)	3.25
C(3) ... C(10)	2.74	C(10) ... O(1)	2.98
C(3) ... O(6)	2.97	C(11) ... C(3')	2.82
C(12) ... Br	3.95	C(11) ... O(1)	3.91
C(12) ... O(3)	3.35	O(3) ... O(6)	3.65
C(12) ... C(3)	3.48		

TABLE 4

Intermolecular distances (<4Å)

O(5) ... Cl_I	3.20	C(5) ... $C(13)_{IV}$	3.72
C(11) ... $O(1)_{II}$	3.38	O(5) ... $C(5')_V$	3.75
C(11) ... Cl_{II}	3.43	O(5) ... $O(2)_{VI}$	3.75
O(3) ... $C(13)_I$	3.44	O(6) ... $C(13)_{IV}$	3.76
O(3) ... $C(12)_{III}$	3.50	O(3) ... $O(4)_I$	3.86
O(4) ... $C(10)_{IV}$	3.50	O(2) ... $C(10)_{III}$	3.88
C(9) ... $C(13)_{IV}$	3.51	C(8) ... $C(13)_{IV}$	3.89
C(3') ... $O(5)_V$	3.54	C(3) ... $C(13)_{IV}$	3.89
O(5) ... $C(12)_{VI}$	3.55	O(2) ... $C(5')_{III}$	3.90
C(4) ... $C(13)_{IV}$	3.56	C(5') ... Cl_I	3.91
C(11) ... $O(5)_V$	3.61	C(2') ... Br_{IV}	3.93
C(4') ... Cl_I	3.67	O(2) ... $C(13)_{IV}$	3.94
C(3') ... $C(12)_{III}$	3.67	O(3) ... $C(10)_{III}$	3.95
C(3') ... Br_{VI}	3.68	C(12) ... $C(10)_{III}$	3.99
C(13) ... $C(10)_{IV}$	3.69		

The subscripts refer to the following positions:

I	x, y, 1 + z	IV	$-x, \frac{1}{2} + y, -z$
II	$-1 - x, \frac{1}{2} + y, -z$	V	$-1 - x, \frac{1}{2} + y, 1 - z$
III	$-x, \frac{1}{2} + y, 1 - z$	VI	$-1 + x$, y, z

TABLE 5

Valency Angles

O(1)C(2)C(3)	108°	C(7)C(8)C(9)	126°
C(2)C(3)C(9)	102	C(7)C(8)O(1)	123
C(2)C(3)O(3)	127	O(1)C(8)C(9)	112
C(9)C(3)O(3)	132	C(8)O(1)C(2)	109
C(3)C(9)C(4)	132	O(1)C(2)C(6')	113
C(3)C(9)C(8)	110	O(1)C(2)C(2')	106
C(8)C(9)C(4)	118	C(3)C(2)C(6')	110
C(9)C(4)C(5)	114	C(3)C(2)C(2')	118
C(9)C(4)O(2)	120	C(2')C(2)C(6')	103
C(5)C(4)O(2)	125	C(2)C(2')C(3')	128
C(4)O(2)C(12)	117	C(2)C(2')O(6)	107
C(4)C(5)C(6)	124	C(3')C(2')O(6)	119
C(4)C(5)Br	114	C(2')C(3')C(4')	117
C(6)C(5)Br	122	C(3')C(4')O(5)	125
C(6)O(4)C(13)	115	C(3')C(4')C(5')	118
C(5)C(6)C(7)	127	C(5')C(4')O(5)	116
C(5)C(6)O(4)	125	C(4')C(5')C(6')	108
C(7)C(6)O(4)	109	C(5')C(6')C(2)	116
C(6)C(7)C(8)	110	C(5')C(6')C(10)	107
C(6)C(7)Cl	128	C(2)C(6')C(10)	105
C(8)C(7)Cl	120	C(2')O(6)C(11)	115

TABLE 6

Standard deviations of the final atomic coordinates (Å)

Atom	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$
C(2)	0.022	0.035	0.025
C(3)	0.023	0.042	0.026
C(4)	0.021	0.033	0.027
C(5)	0.020	0.042	0.022
C(6)	0.021	0.048	0.021
C(7)	0.024	0.035	0.027
C(2')	0.025	0.036	0.036
C(3')	0.025	0.037	0.031
C(4')	0.023	0.036	0.026
C(5')	0.027	0.046	0.030
C(6')	0.028	0.042	0.025
C(8)	0.022	0.047	0.024
C(9)	0.021	0.037	0.023
C(10)	0.033	0.042	0.033
C(11)	0.041	0.057	0.041
C(12)	0.043	0.056	0.048
C(13)	0.033	0.041	0.035
O(1)	0.015	0.027	0.019
O(2)	0.015	0.023	0.017
O(3)	0.018	0.030	0.017
O(4)	0.016	0.034	0.015
O(5)	0.022	0.028	0.022
O(6)	0.018	0.029	0.022
Cl	0.006	0.012	0.007
Br	0.006	0.009	0.005

TABLE 7

Anisotropic temperature-factor parameters ($10^5 b_{ij}$).

	b_{11}	b_{22}	b_{33}	b_{12}	b_{23}	b_{13}
C(2)	818	919	1142	-1851	521	450
C(3)	873	2290	1531	-1346	-431	724
C(4)	705	399	1796	-254	-244	547
C(5)	1134	652	1490	-508	-1166	1216
C(6)	1436	548	1520	324	631	2204
C(7)	1005	745	1549	-1777	823	368
C(2')	1179	722	4097	820	2904	2866
C(3')	1133	1643	2373	-1088	282	1909
C(4')	1205	1598	1728	1361	322	1788
C(5')	1467	1739	2261	3588	1019	1925
C(6')	1507	2937	1102	-791	1917	1365
C(8)	684	5057	1062	-1773	382	669
C(9)	674	2143	1206	372	1324	804
C(10)	2242	997	2230	1736	-990	2102
C(11)	1916	4230	2371	2172	-486	447
C(12)	2413	3793	3383	2302	-724	1957
C(13)	2039	1367	2722	-2200	1097	2283
O(1)	483	3980	1706	-599	211	746
O(2)	986	411	1905	209	-288	1015
O(3)	1537	1820	1321	-928	-720	974
O(4)	2036	1238	1986	618	748	3044
O(5)	1854	2839	2406	-222	460	2493
O(6)	1148	2568	3094	795	-880	2572
Cl	1076	2866	1270	-221	-515	807
Br	967	3148	2052	-636	267	1489

Table 8 5-Bromogriseofulvin

Final observed and calculated values of the structure factors.

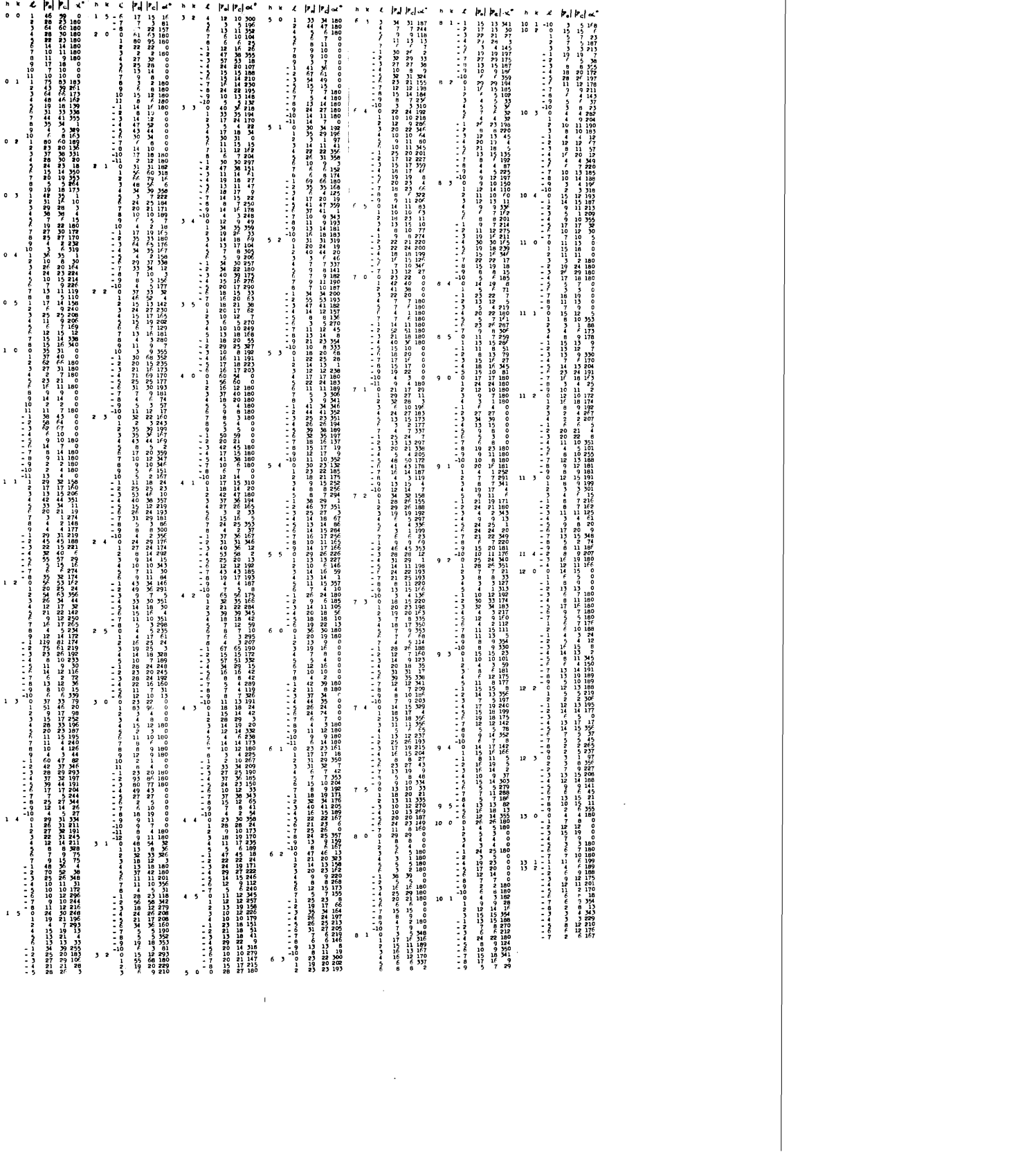


TABLE 9

Displacements (Å) of atoms from the mean plane through the aromatic system C(4), C(5), C(6), C(7), C(8), C(9), C(3), O(2), Br, O(4), Cl, and O(1).

C(4)	0.10
C(5)	-0.07
C(6)	-0.03
C(7)	0.11
C(8)	0.06
C(9)	0.01
C(3)	-0.21
O(2)	0.08
Br	-0.02
O(4)	-0.06
Cl	-0.04
O(1)	0.08
O(3)	-0.40
C(2)	-0.09
C(4')	-0.41
O(5)	-0.46

P A R T III

THE CONFORMATION OF THE BICYCLO (3,3,1) NONANE SYSTEM: X-RAY ANALYSIS OF 1-p-BROMOBENZENESULPHONYL-OXYMETHYL-5-METHYLBICYCLO (3,3,1) NONAN-9-OL

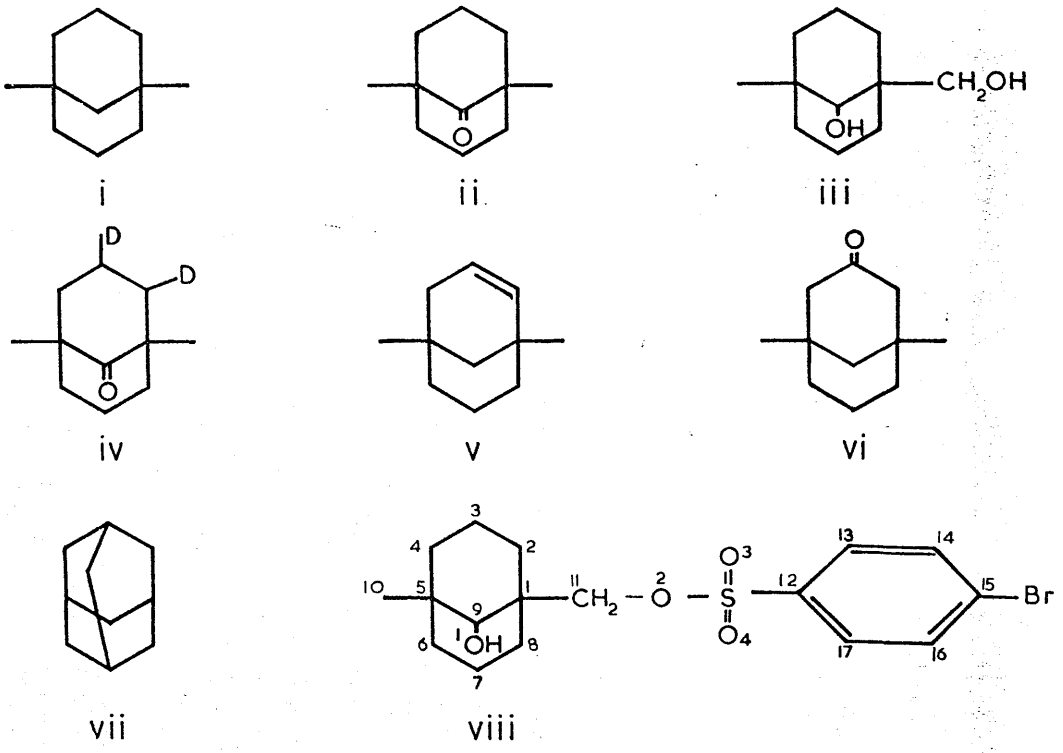

i
ii
iii
CH2OH
OH
O
iv
v
vi
D
D
O
O
vii
viii
3
4
2
10
5
1
11
CH2
2
O
O3
S
O4
12
13
14
15
Br
9
1
OH
6
8
7
17
16

FIG. 12.

3.(1). Introduction.

When molecular models of the bicyclo (3,3,1) nonane system are constructed it is observed that certain strong hydrogen-hydrogen interactions will exist in the molecule no matter which conformation the two rings adopt. Examples of possible conformations are shown in Fig. 11. They are (A) a twin-chair, (B) a boat-chair, (C) a twin-boat and (D) a twin twist-boat.

Eliel (1962) stated that there would be an intolerable transannular interaction between the axial hydrogen atoms at C(3) and C(7) if the molecule adopted conformation (A), and suggested that the molecule existed in conformation (B), even although there would also be some fairly unfavourable interactions involved in this case as well.

The infra-red spectra of various bicyclo (3,3,1) nonane derivatives were examined in order to investigate the conformation of the system (Brown et al., 1964). Some typical examples of these compounds are shown in Fig. 12. Of these compounds, (I), (II), and (III) were found to exhibit absorption bands near 2990 and 1490 cm.$^{-1}$ which were attributed to methylene group - methylene group interactions.

If the molecule adopted the boat-chair conformation, as suggested by Eliel, it would be possible to explain these bands in case (I) in terms of C(3) - C(9) or C(7) - C(9)

methylene interactions. However, that these are not the causative interactions is shown by the fact that the ketone (II) also shows these absorption peaks. This leads to the conclusion that the spectra can only be interpreted in terms of C(3) - C(7) methylene interactions present when the molecule adopts the presumably unfavourable twin-chair conformation.

This fact is further substantiated by examination of the infra-red spectra of compounds in which this C(3) - C(7) interaction is relieved. Thus, introduction of a double bond into the system as in (V) or the insertion of a carbonyl group at C(3) or C(7) as in (VI) would be expected to nullify these absorption bands. Experimentally, this proved to be the case.

The bisdeutero-ketone (IV) showed a reduction of a factor of one half in the intensity of the 1490 cm.$^{-1}$ band. This is due to the replacement of the scissoring band at C(3) by a comparable CDH band elsewhere in the spectrum. The 2990 cm.$^{-1}$ band for this compound thus appeared as an indistinct shoulder on the high-frequency side of the main C-H stretching absorption.

The final piece of spectroscopic evidence is obtained from the beautifully symmetric structure, adamantane, shown in Fig. 12 (VII). This structure is completely free from

strain, the unfavourable C(3) - C(7) transannular interaction having been removed by substitution of a bridge carbon atom between these two atoms. As expected, there were no absorption bands in the neighbourhood of 2,990 and 1,490 $cm.^{-1}$.

These characteristic maxima appear in the spectra both in solution and in the solid state, indicating that the molecule has the same conformational skeleton in both these circumstances. It was therefore permissable to accept results from x-ray analysis for consolidation of the above findings.

In order to introduce a heavy atom into the bicyclo (3,3,1) nonane system, the primary bromobenzene-p-sulphonate of compound (III) was prepared. This is shown in Fig. 12 (VIII) and the systematic name for it is 1-p-bromobenzene-sulphonyloxymethyl-5-methylbicyclo (3,3,1) nonan-9-ol, although it will subsequently be referred to simply as BROS.

3.(2). Experimental.

Rotation, oscillation, Weissenberg and precession photographs were recorded using copper - K_α ($\lambda = 1.5418\text{Å}$) and molybdenum - K_α ($\lambda = 0.7107\text{Å}$) radiations. The unit cell parameters were estimated from rotation and precession photographs and, in the latter case, the unit cell edges

and angles were derived from the reciprocal cell parameters by the conversion formulae for triclinic crystals as listed by Buerger (1942). The intensities were recorded using a small crystal completely bathed in a uniform x-ray beam and no adjustments were made to account for absorption. The data was collected on zero layer and equi-inclination upper layer Weissenberg photographs obtained by rotating the crystal about the a - and c-axes, the reciprocal lattice nets Okl and 1kl being registered in the former case and hko, ------, hk7 in the latter. One further zone, hol, was recorded by means of a timed series of precession photographs. Visual methods of intensity estimation were used, all Weissenberg data having been registered using Robertson's multiple film technique (1943). In all, 2176 intensity estimations were made, of which 1633 were from independent reflections.

The intensity values were corrected for Lorentz, polarisation and the rotation factors appropriate to upper layers and the values of the structure amplitudes obtained by application of the mosaic crystal formulae.

The various zones of $|F_o|$'s were all placed on an approximately absolute scale by correlation with the values of $|F_c|$ obtained from the first structure factor results.

The density of the crystals was obtained by flotation methods using potassium iodide solutions.

3.(3). Crystal Data.

$C_{17}H_{23}O_4S\,Br$ — $M = 403.3$

Triclinic — $a = 7.40 \pm 0.02\text{Å}$

$b = 12.06 \pm 0.02\text{Å}$

$c = 11.34 \pm 0.05\text{Å}$

$\alpha = 112^{\circ}30'$

Volume of the unit cell $\beta = 109^{\circ}31'$

$= 862\text{Å}^3$ $\gamma = 72^{\circ}41'$

For $z = 2$, D(calculated) = 1.55 g./cc.

D(observed) = 1.53 g./cc.

F(000) = 416

Linear absorption coefficient for x-rays ($\lambda = 1.542\text{Å}$),

$\mu = 48.1$ cm.$^{-1}$.

Since the crystal is triclinic there are no systematically absent spectra.

It was decided to proceed with the analysis on the assumption that the space group is $P\bar{1}$. If this had been an erroneous choice it would have shown up in subsequent electron density maps.

3.(4). Location of the Heavy Atom Positions.

The Patterson function to be employed in the case of a crystal belonging to the triclinic system is

$$P(uvw) = \frac{2}{V_c} \sum_{0}^{\infty}\sum_{-\infty}^{\infty}\sum_{-\infty}^{\infty}(|F(hkl)|^2 \cos 2\pi(hu + kv + lw)) \quad \text{---- (3.1)}$$

This equation can be simply reduced to two-dimensional expressions.

Since there are two molecules per unit cell and two heavy atoms in each molecule, principal vectors between four sets of atomic coordinates arise. The bromine coordinates are designated $(x_B\ y_B\ z_B)$ and $(\bar{x}_B\ \bar{y}_B\ \bar{z}_B)$ and the sulphur coordinates by $(x_S\ y_S\ z_S)$ and $(\bar{x}_S\ \bar{y}_S\ \bar{z}_S)$.

The interactions between these give rise to the following vectors -

(i)	$2x_B$	$2y_B$	$2z_B$
(ii)	$2x_S$	$2y_S$	$2z_S$
(iii)	$x_B + x_S$	$y_B + y_S$	$z_B + z_S$
(iv)	$x_B - x_S$	$y_B - y_S$	$z_B - z_S$

Vectors (i) and (ii) are single weight peaks and the other two are double weight.

The Okl projection was the first Patterson map to be studied. The symmetry of this projection, as with those down the other two axes, is p2. This symmetry infers that the series need only be summed over half of the unit cell area. This being the case, the function was evaluated from $w = 0$ to $w = 1$ and from $v = 0$ to $v = \frac{1}{2}$. The map is shown in Fig. 13.

The bromine-bromine vector showed up clearly and is marked N on the map. The two bromine-sulphur vectors were also readily distinguished and they are indicated by P and Q respectively. It was not found possible at this stage to identify positively the sulphur-sulphur peak, but calculation of the sulphur coordinates showed it had to be placed at R.

From this map the y- and z-coordinates of the heavy atoms were deduced. No account was taken of peak R in the estimation of the sulphur position. The coordinates were -

$y/b_{Br} = 0.0040$ $\quad z/c_{Br} = 0.2507$

$y/b_{S} = 0.2899$ $\quad z/c_{S} = 0.5361$

The hko and hol Patterson maps were computed, but due to serious overlapping of vectors, no solution for the x-coordinates of the above two atoms could be obtained.

It was then deemed necessary to calculate the three-dimensional Patterson function using the unscaled data. From this map the three coordinates of both atoms were unambiguously settled. The section at $w = \frac{1}{2}$ through the distribution on which the bromine-bromine peak (marked S) reached its maximum is shown in Fig. 14 as a representative example of the Patterson map.

Normally more accurate coordinates would be expected from a three-dimensional than a two-dimensional vector map.

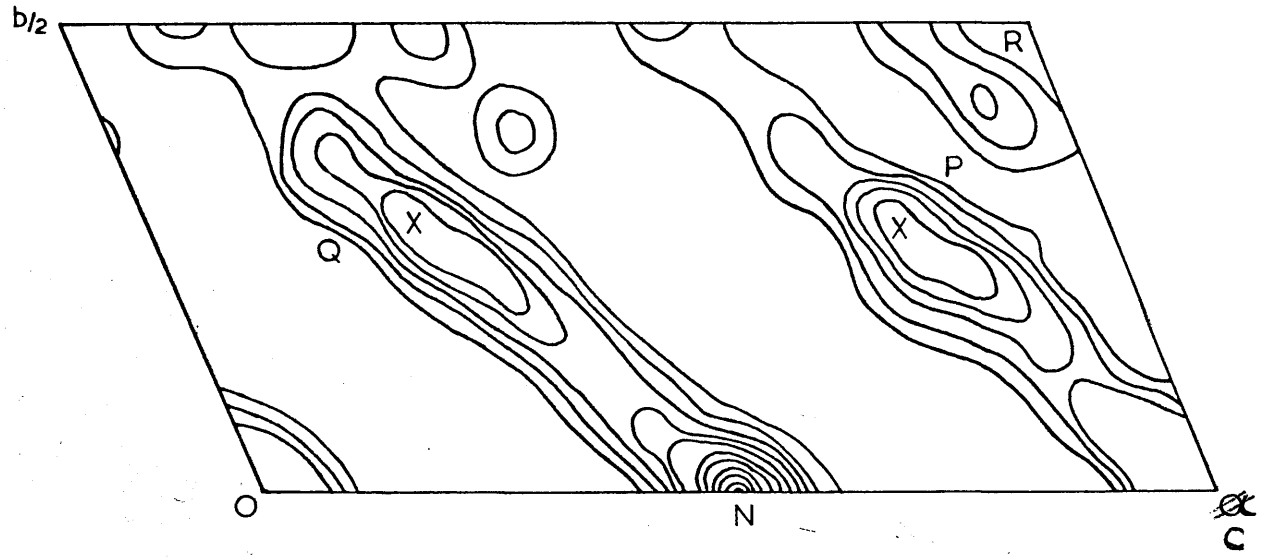


Fig. 13 BROS.

Patterson projection along the a-axis. Contour scale arbitrary. Origin peak contours omitted.

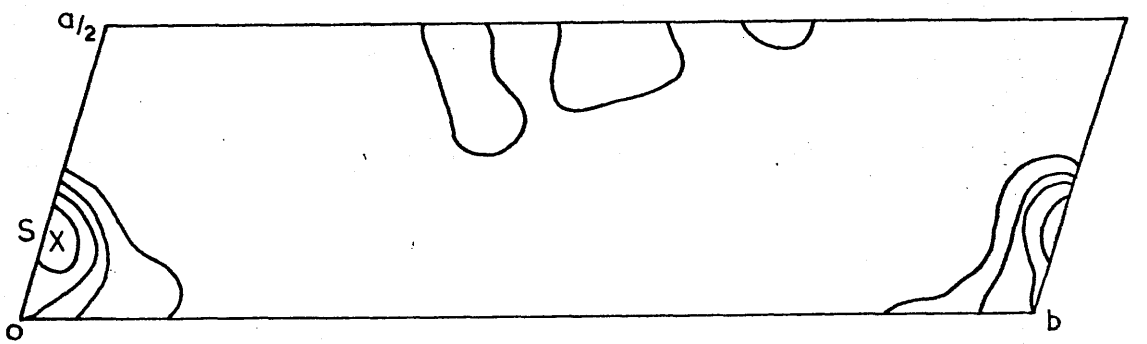


Fig. 14 BROS.

Section at w = $\frac{1}{2}$ through three-dimensional Patterson map. Contours at arbitrary intervals.

However, the fact that the former distribution was calculated using unscaled data as coefficients possibly reduces any such additional accuracy. With this in mind it was decided to accept the mean value of the y- and z-coordinates calculated by both methods.

The coordinates so arrived at were -

$x/a_{Br} = 0.0714$ $y/b_{Br} = 0.0044$ $z/c_{Br} = 0.2551$

$x/a_{S} = 0.2880$ $y/b_{S} = 0.2875$ $z/c_{S} = 0.5330$

3.(5). Solution of the Structure.

Since the bromine and sulphur atoms are known to be para-related across the benzene ring it was possible, using standard values for valency bond lengths and trigonometric distance formulae, to calculate the coordinates of the two carbon atoms directly bonded to the heavy atoms. The coordinates of these four atoms were thus used in a first phasing calculation.

It was of interest to establish approximately what fraction of the structure factors would be expected to be correctly sign-determined by using this group of atoms in the phasing calculation. Sim (1957) has deduced a relationship between this fraction and the value of r, where r is the ratio of the root-mean-square contributions of the located to the unlocated atoms for space groups P1 and

$P\bar{1}$. The fraction has been tabulated for a range of values of $\underline{r}$.

In this instance the value of $\underline{r}$ is 1.55 which indicates that of the order of 85% of the structure factors will have been allotted the correct sign.

These coordinates and an assumed uniform isotropic temperature factor of $\alpha = 3.0$ were employed in the first structure factor calculation. The value of the discrepancy, R, summed over all the observed terms was 41.4%. At this stage all the $|F_o|$ values were put on a very approximately absolute scale, by correlating them with the corresponding $|F_c|$ data. However, since the coordinates of only four atoms had been included in the calculation, no attempt was made at this stage to average out the $|F_o|$ values of reflections common to more than one zone. The data collected by rotation about the c-axis appeared to be the best and initially the structure factors for Fourier calculations were chosen from these zones when common reflections existed.

Of the 1633 independent structure amplitudes, 1521 (93%) were deemed to have been safely sign-determined in the structure factor calculation. These were employed as Fourier coefficients in a first electron density distribution evaluated at grid-points from x = 0 to x = 1, y = 0 to y = 1

and z = 0 to z = $\frac{1}{2}$, the summation being calculated in sections parallel to (001).

From the resulting map all the atoms in the structure (excepting hydrogen atoms) were clearly resolved. There were few spurious peaks in the distribution and it was thought that all of these could be discounted since the molecular structure was already known. It was immediately obvious that the molecule did, in fact, adopt the hopefully anticipated chair - chair conformation as in Fig. 11(a). However, at first sight, it appeared that the two six-membered chair rings of the bicyclononanol were rather distorted, because the plane containing atoms C(2) C(3) C(4) was not parallel to that defined by C(6) C(7) C(8), as it should be in an ideal model. Moreover, this distortion was apparently due rather to a pushing-out of atoms C(3) and C(7) leading to a flattening of the two rings, than to a lateral displacement of the two three-atom planes defined above. The conclusion as to the distortion could only be taken as tentative, however, at this early stage of the analysis. The coordinates of all twenty three atoms were calculated by the method due to Booth (1948).

The atomic coordinates and a uniform value of α = 3.0 were then utilised in the evaluation of a second set of structure factors. The discrepancy calculated from all

observed terms was 27.2% i.e. an overall decrease in R of 14.2% or 0.75% per atom. 1577 of these reflections were regarded as safely sign-determined and were used in the computation of a new Fourier series.

The atoms in this map were all clearly resolved and the fact that the chair-rings were distorted was confirmed. Most of the spurious electron density had disappeared but one large peak appeared within the bonded distance to C(9) and on the opposite side of the C(1) C(9) C(5) plane from O(1). This was the first indication that the structure was disordered.

Since C(9) is the only asymmetric atom in the molecule it follows that the (+)- and (-)- molecules are superimposable except for the hydroxyl group at this atom. Two peaks appeared on either side of the C(1) C(9) C(5) plane and obviously both represented atoms bonded to C(9). It follows from these facts that the (x y z) and ($\bar{x}$ $\bar{y}$ $\bar{z}$) equivalent positions are not each uniquely occupied by one enantiomorphic form of the molecule. It was decided to investigate this disorder further, and in particular to ascertain whether it was completely random or whether one equivalent position was preferentially occupied by one enantiomer.

Some structure factor calculations were then performed and from these it appeared that both equivalent positions were associated with approximately 50% of each epimer i.e. tentatively, it could be stated that the disorder occurred randomly. To account for this effect it was decided to include the coordinates of both these atoms - O(1) and O(1') - in subsequent structure factor calculations assigning them to a new chemical type of scattering factor equal to half of that of oxygen.

3.(6). Refinement of the atomic parameters.

Using the $|F_c|$ values and accepted signs from the second set of structure factors, a Fourier series was computed. Using this distribution in conjunction with the F_o map previously discussed new coordinates were evaluated for all the atoms using the back-shift correction method (Booth 1946) and alterations were made in the temperature factor values. The overall discrepancy fell by 2.4% to 24.8%.

After three further cycles of this method of refinement employing 1586, 1610 and 1625 structure factors as Fourier coefficients, respectively, the R-factor had fallen to 20.1%.

A comparison of the relative peak heights of atoms O(1) and O(1') on the various F_c maps, led to an attempt to

refine the site occupancy of these two atoms by adjustment of their scattering factors with respect to one another during the course of the back-shift correction refinement. Atom O(1) was included in the various cycles with a scattering factor equal to 0.6 times, 0.55 times andthen again 0.5 times that of oxygen with suitably adjusted values for O(1'). From this it appeared that the best agreement could be obtained when the last of these three values for the scattering factors was employed, which corresponds to the case when the sites are randomly occupied. A final decision as to this fact was postponed till the completion of refinement.

Before continuing refinement by the method of least squares it was necessary to place all the $|F_o|$ values on the same scale and to average out the values for reflections which were common to more than one zone. This was performed, and intensities were re-estimated in cases where there was a sizeable discrepancy between the $|F_o|$ values.

The weighting system first employed was W_1 (see section 1.(3).(iii)) and $|F^*|$ was 10. After the first structure factor calculation, R was 19.5% - the drop of 0.6% being accounted for by the averaging of the $|F_o|$ values described above. After six cycles the discrepancy was 12.9% and the near-constancy of $\sum w\Delta^2$ showed that refinement

by this method was effectively complete. A change was made to weighting scheme, W_2, but after two cycles, the value of R was still 12.9%. This was the limit of refinement. The progress of the structure analysis and refinement is indicated in Table 10.

Using the final set of least-squares structure factors a three-dimensional difference map was computed in an attempt to locate the positions of hydrogen atoms. Although a fair number of positive peaks showed up in the distribution it was found impossible to assign a set of these to hydrogen sites.

The theoretical scattering factors for carbon, oxygen and bromine were those used in the 5-bromogriseofulvin analysis. For sulphur those of James and Brindley (1931) were employed.

3.(7). Results.

The final atomic coordinates for one molecule are listed in Table 11. From these coordinates were evaluated the valency bond lengths, and the intramolecular and intermolecular non-bonded distances which are less than 4Å. These data are listed in Tables 12, 13 and 14 respectively. The valency bond angles were also determined from the atomic coordinates and are shown in Table 15.

The standard deviations of the coordinates were obtained from the least squares residuals in the usual manner (see section 1.(5).). They are shown in Table 16. From these results it can be established that the following are the e.s.d's. of the indicated bond lengths:-

Bond	e.s.d. (Å)
C - C	0.03
C - O	0.02
C - O($\frac{1}{2}$)	0.03
C - S	0.02
C - Br	0.02
S - O	0.01
S - Br	< 0.01

The average e.s.d. of a valency angle is about 2°.

Table 17 shows the various b_{ij} parameters necessary for the definition of the atomic anisotropic vibrations.

The values of $|F_o|$ and $\pm |F_c|$ are shown in Table 18 for all reflections whose structure amplitudes are equal to or greater than the observational minimum value.

The final structure factors were employed as coefficients in the evaluation of a last F_o map. The electron-density distribution over one molecule is shown in Fig. 15 by means of superimposed contour sections drawn parallel to (001) and on which the alternative C(9) - O(1) and C(9) - O(1') bonds

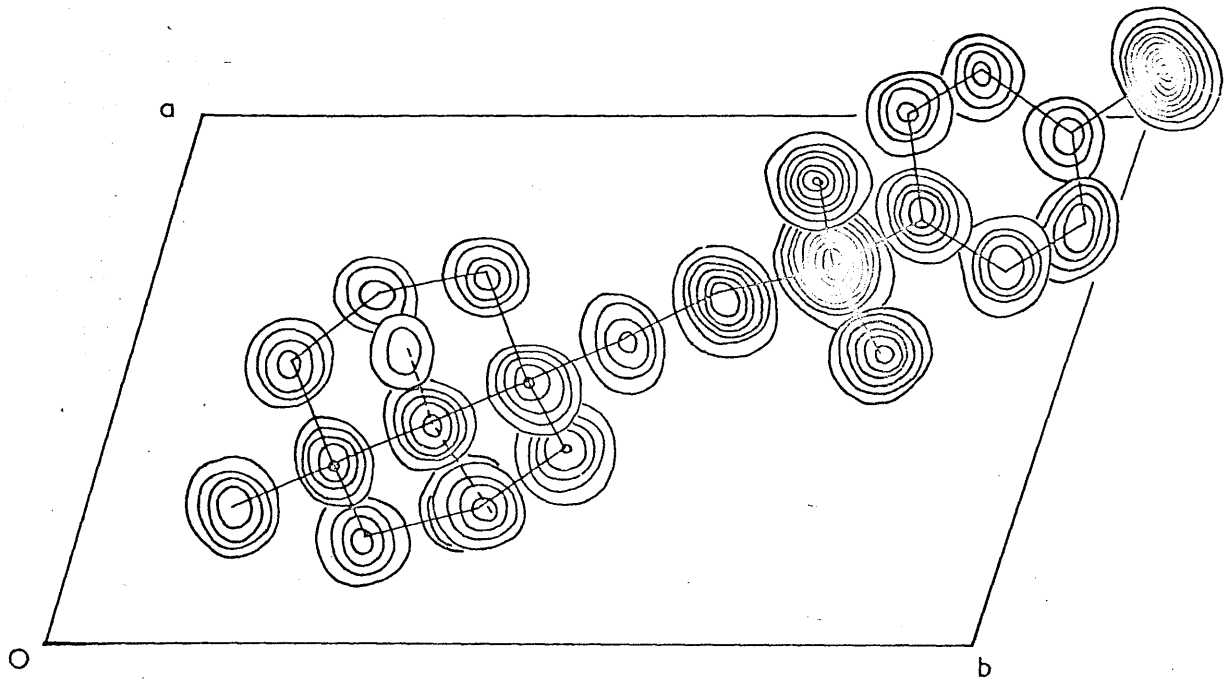


Fig. 15 BROS.

Final superimposed contour section electron density map drawn parallel to (001). Contour interval is 4e/Å^3 for bromine, 2e/Å^3 for sulphur and 1e/Å^3 for carbon and oxygen.

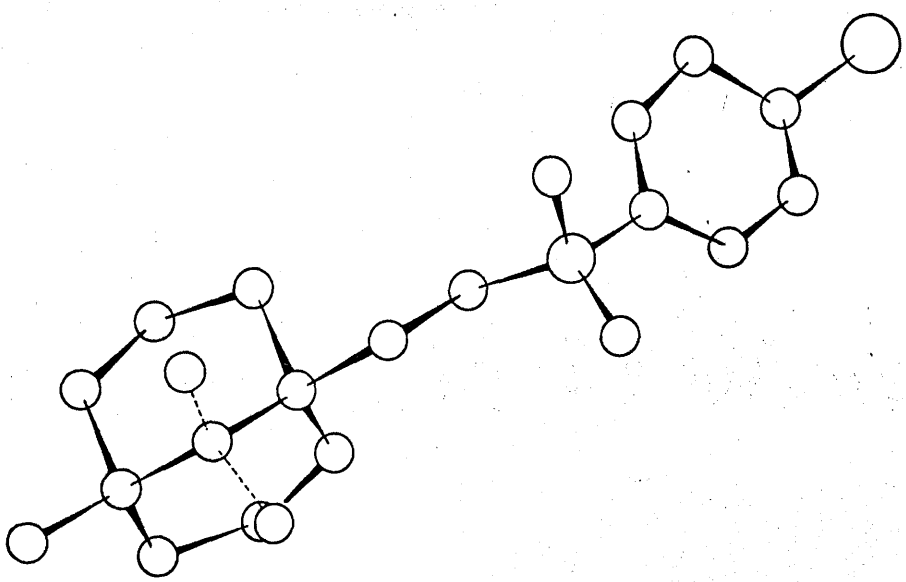


Fig. 16 BROS.

Atomic arrangement corresponding to Fig. 15.

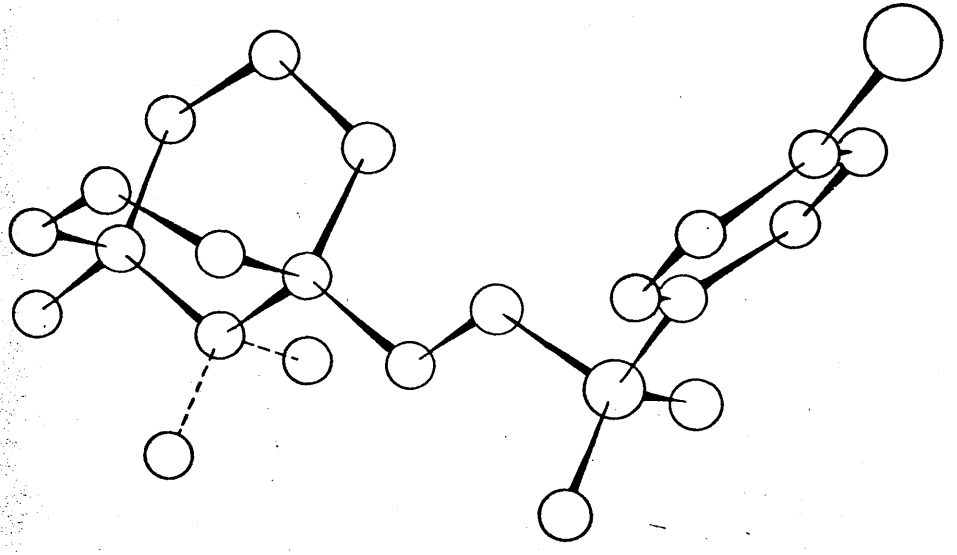


Fig. 17 BROS.

Atomic arrangement as viewed down the a-axis.

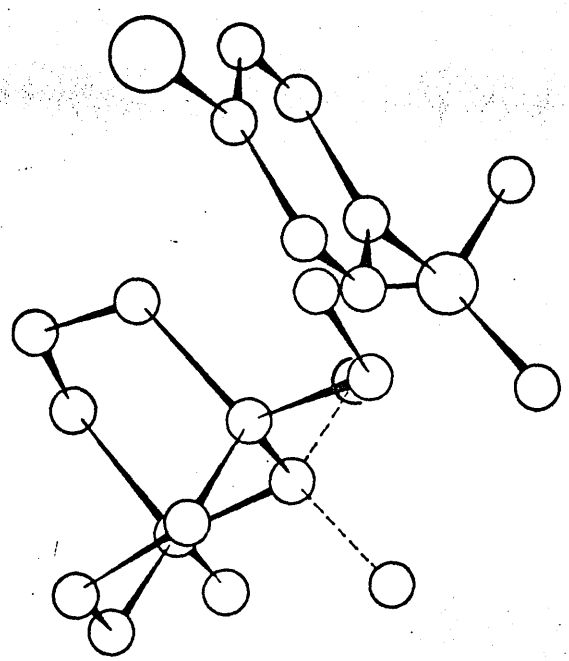


Fig. 18 BROS.

Atomic arrangement as viewed down the b-axis.

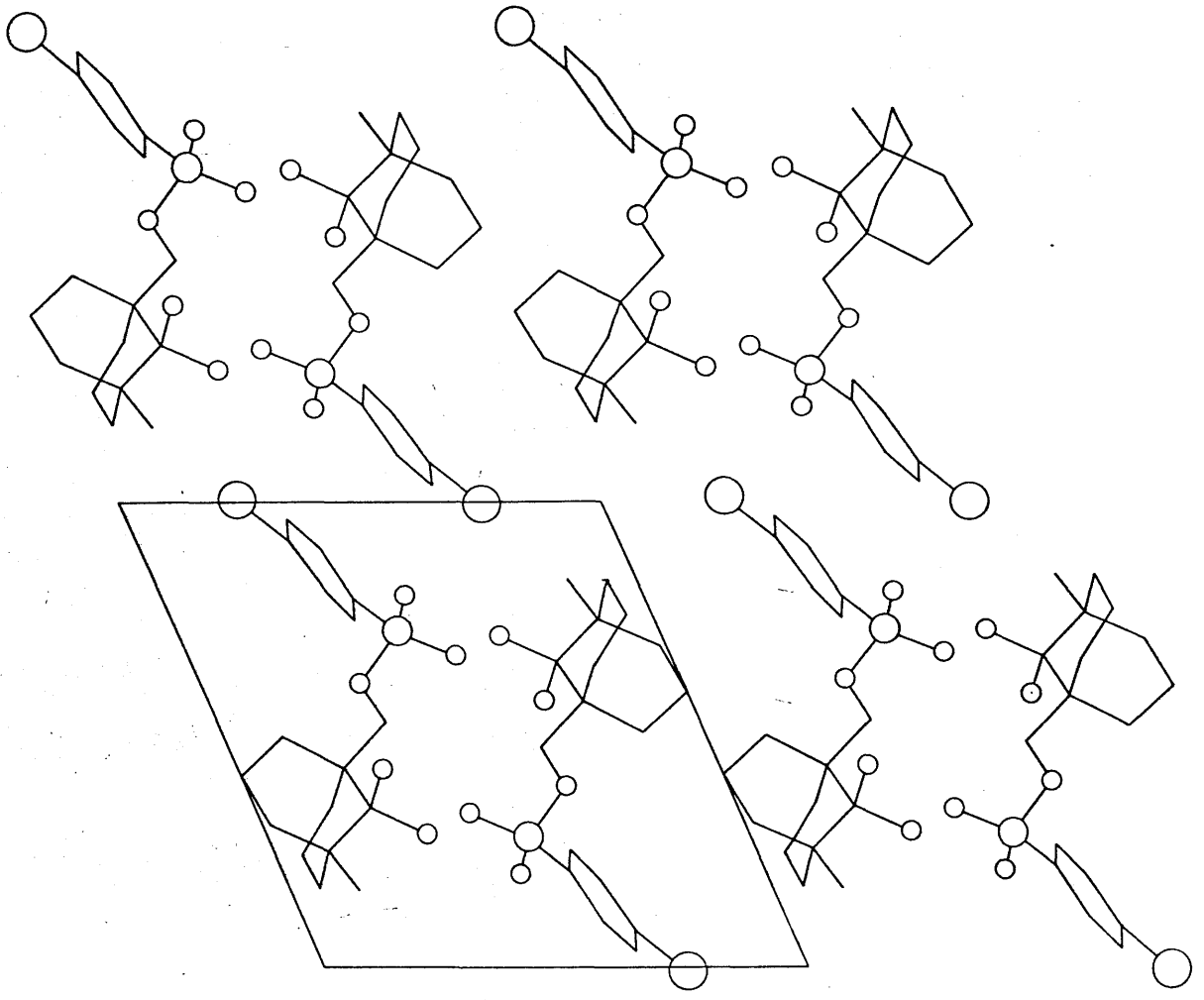


Fig. 19 BROS.

Packing diagram as viewed down the a-axis.

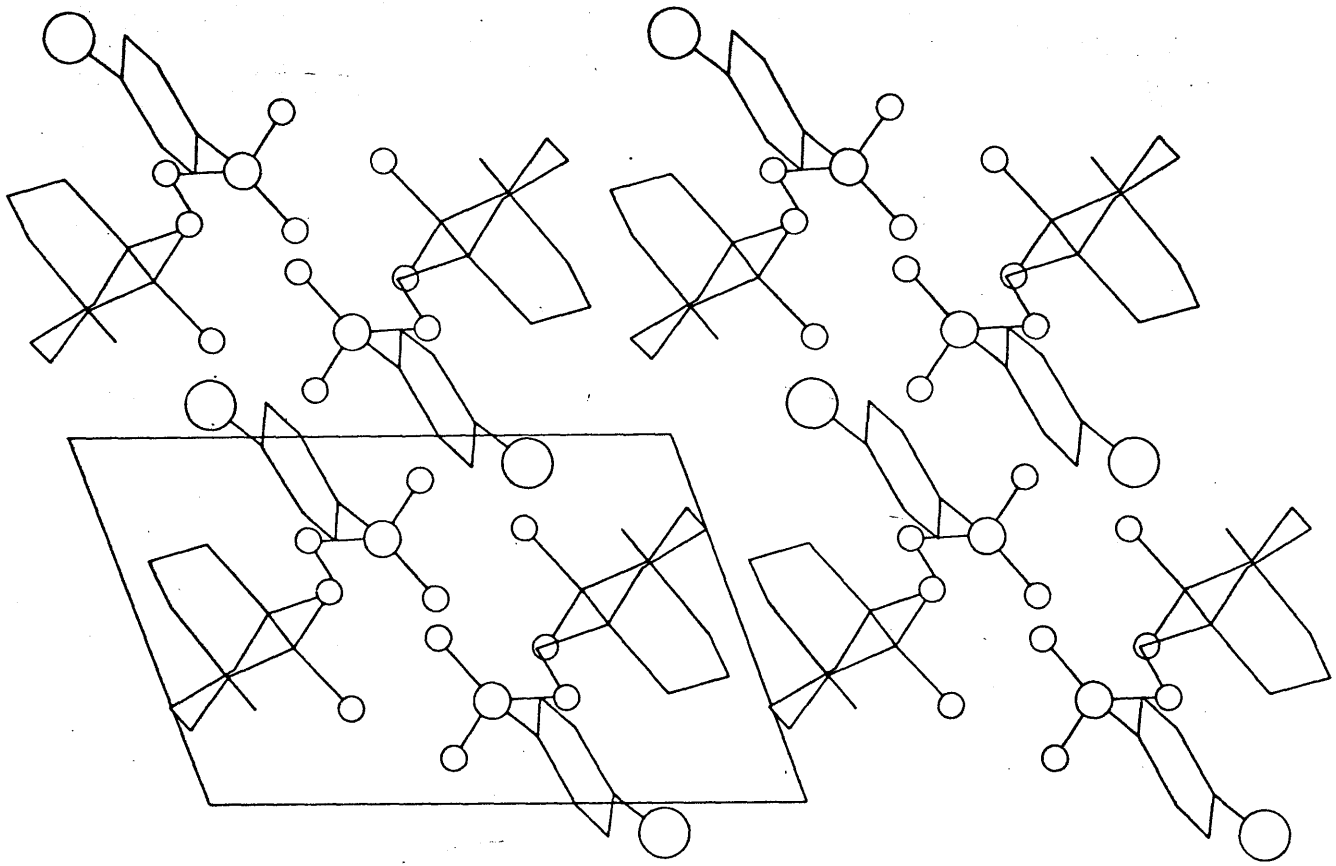


Fig. 20 BROS.

Packing diagram as viewed down the b-axis.

are shown by broken lines. The corresponding atomic arrangement of the molecule is shown in Fig. 16. The atomic arrangement in the molecule as viewed in projection down the a- and b-axes is portrayed in Figs. 17 and 18 respectively. From these three last-mentioned diagrams it is immediately obvious that the molecule adopts the twin-chair conformation.

The packing of the molecules was viewed in projection down each of the three axes. Of these, those parallel to (100) and (010) gave clear non-overlapping diagrams and are depicted in Figs. 19 and 20 respectively.

Various mean plane calculations were performed using the final atomic coordinates. These will be discussed in section 3.(8). The atomic deviations from these planes are delineated in Table 19.

3.(8). Discussion.

The main criterion which had to be established in this analysis was the conformation of the two six-membered rings in the bicyclo (3,3,1) nonane system. The three-dimensional Fourier maps and molecular arrangements shown in Figs. 16 - 18 prove beyond all doubt that the rings are both present in the chair conformation. Further evidence of this is given by the mean plane deviations listed in Tables 18a and 18b.

It is seen from the tabulated results that, in both rings, C(9) lies on the opposite side of the molecular planes from the atoms C(7) and C(3).

It is of interest to note that, by using bond moment and bond polarisability data, Eckert and Le Fèvre (1964) have been able to show that in solution, at least 50% of the molecules of the analagous compound pseudo-pelletierine exist in the twin-chair conformation. This compound has a carbonyl group at C(3) and thus would be less strained than BROS.

It was stated earlier that the chair conformations in both rings of BROS deviated markedly from ideality. This can now be proved quantitatively by the following facts -

(i) If the chairs were ideal all of the valency bond angles around the bicyclic system would be tetrahedral within the limits of experimental error. The angles around atoms C(1), C(5) and C(9) do, in fact, average out at 110°, but the mean internal angle at C(2), C(3), C(4), C(6), C(7) and C(8) is 114° - significantly greater than tetrahedral. This indicates that there must be a flattening of the rings at these latter atomic positions.

(ii) If a Dreiding model of the system is constructed, the distance apart of C(3) and C(7) is found to be 2.52Å. That the rings are considerably flattened is shown by the fact that, in actuality, this distance is 3.06Å.

(iii) If the twin-chair system were ideal it would follow that C(9) would be the same distance above the C(1) C(6) C(8) C(5) plane as C(7) is below it. From Table 18a these distances are found to be 0.72Å and 0.45Å respectively, proving that C(7) is situated nearer to the mean plane than in the ideal model. An identical argument applies to the fact that C(9), from Table 19b, is seen to lie 0.71Å above the C(1) C(2) C(4) C(5) plane whereas C(3) is 0.51Å below it.

(iv) In the ideal bicyclo (3,3,1) nonane system plane C(11) C(1) C(9) C(5) C(10) is parallel to planes C(2) C(3) C(4) and C(6) C(7) C(8). The equations of these planes were calculated and the interplanar angles derived. The five-atom plane makes an angle of 163° with plane C(2) C(3) C(4), and of 162° with plane C(6) C(7) C(8). This again points to the fact that there is a flattening of the rings at C(3) and C(7).

The rings are, of course, flattened to the same extent at C(3) and at C(7). This is shown by the fact that C(3) is displaced by 1.54Å from the C(11) C(1) C(9) C(5) C(10) plane, whereas C(7) is situated the insignificantly different distance of 1.50Å on the other side of the plane. These values are taken from Table 19c. This fact is also proved by the near-equality of the angles mentioned in (iv) above.

The possibility also exists that some displacement from ideality might take place by a sideways movement of C(2) C(3) C(4) and C(6) C(7) C(8) in opposite directions and parallel to the plane described in Table 19c. If this were the case there would be a marked difference between the C(2) - C(6) and the C(4) - C(8) non-bonded distances. Table 13 shows that both these distances are 3.65Å, so that this type of deviation is not appreciably involved in the relief of strain.

Recently the results of the x-ray analysis of 3-azobicyclo (3,3,1) nonane hydrobromide (Dobler, 1963) have become available. The cation of this structure consists of the basic skeleton of the bicyclo (3,3,1) nonane system with a nitrogen atom substituted for C(3).

Dobler's measurements and conclusions agree with those discussed above. The molecule adopts a twin-chair conformation and the chairs are distorted from ideality by a flattening of the rings at C(7) and the nitrogen atom. He found that the average valency angle at C(2), C(4), C(6), C(7), C(8) and N is 113° and that the N - C(7) separation is 3.1Å leading to a hydrogen-hydrogen distance of 1.8Å. There is no lateral displacement from ideality of N and C(7) parallel to the C(1) C(5) C(9) plane, and thus no steric strain is relieved in this manner.

Referring again to Table 18, it was calculated that the angle in BROS between plane (a) and plane (b) was 113°, that between plane (a) and plane (c), 124° and that between plane (b) and plane (c), also 124°.

The equation of the mean plane of the benzene ring and the sulphur and bromine atoms was calculated as with all previous planes by the method of Schomaker et al. (1959). The deviations from the plane are listed in Table 18d, but none of them can be taken as significant.

Earlier it was mentioned that a decision as to site occupancy of atoms O(1) and O(1') would be made when refinement was completed. The final F_o map gave peak heights of 5.53 and 3.54 electrons /Å^3 for these two atoms, respectively. The corresponding figures from an F_c synthesis were 5.28 and 3.46 electrons /Å^3. These results indicate that the disorder is very nearly random.

The average length of the sp^3-carbon-oxygen bond is 1.48Å which is in agreement with the value of 1.46Å obtained for 5-bromogriseofulvin, described earlier in this thesis.

The mean carbon-carbon distance in the benzene ring, 1.38Å, and the sp^3-carbon-sp^3-carbon bond length, 1.54Å, are both in accord with expected values.

The aromatic carbon-bromine bond length of 1.87Å is in fair agreement with the generally accepted value of about

1.90Å. International Tables for Crystallography Vol. III (1962a) quote this value as 1.85Å, but more recent papers on full three-dimensional refinement give values considerably in excess of this. Kartha (1964) found a value of 1.92Å for this bond length in the analysis of morellin p-bromobenzenesulphonate and Gemmell and Sim (1964) have obtained a distance of 1.91Å in the same ester of α-caryophyllene alcohol. In any event, this bond length is a difficult one to assess, since the position of C(15), being bonded to the bromine atom, is inaccurate due to diffraction effects of the latter atom.

The aromatic carbon-sulphur bond length is 1.72Å and appears to be considerably shorter than 1.765Å found in 4,4'-dichlorodiphenyl sulphone (Sime and Abrahams, 1960), but closer to the value of 1.74Å in zinc p-toluene sulphonate hexahydrate (Hargreaves, 1957). The values given by Kartha (1964) and Gemmell and Sim (1964) are 1.76Å and 1.75Å respectively.

The mean sulphur-oxygen double bond distance is 1.44Å and the sulphur-oxygen single bond has a length of 1.57Å. This is in good agreement with the pattern in potassium ethyl sulphate where these values are 1.46Å and 1.60Å respectively. (Truter, 1958). The theoretical single bond length is 1.69Å and this contraction to about 1.6Å can be

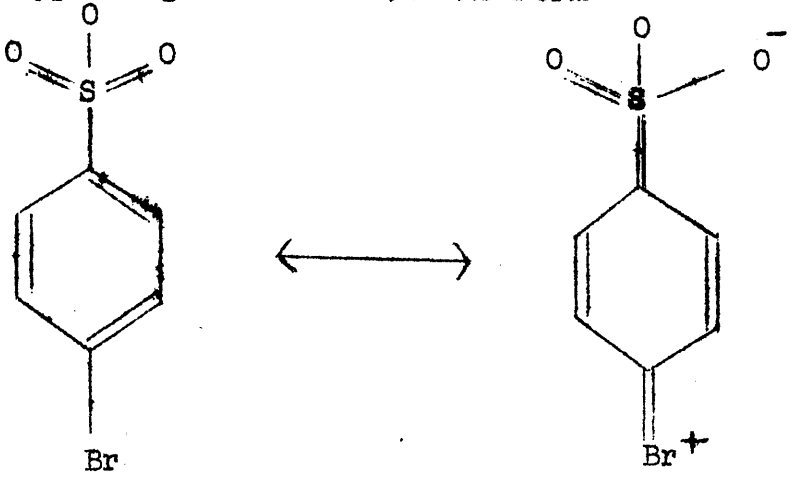
explained by partial double bond character of a formal single bond between the oxygen and sulphur atoms which have different electronegativities, since the sulphur atom can form π-bonds using its 3d-orbitals.

Cruickshank (1961) has shown that the π - bond order of the sulphur - ester oxygen bond in potassium ethyl sulphate is $\frac{1}{4}$ which should give a bond length of about 1.59Å. In addition, the other three sulphur-oxygen bond distances should contract from the double-bond value of 1.49Å to 1.46Å since the other π -bonding orbital of sulphur is shared with only three of the four oxygens, giving these bonds an order of $\frac{1}{4} + \frac{1}{3} = 0.58$. He gives a useful empirical rule that the average sulphur-oxygen bond length in the sulphate and related groups is 1.49Å, but that any sulphur-oxygen bonds which involve a linkage of oxygen to another atom may lengthen by amounts up to about 0.15Å with a corresponding contraction of the other sulphur-oxygen bonds so as to preserve the average.

In the case of BRO3 the average bond length is 1.48Å and individual bonds are expanded to 1.57Å and contracted to 1.44Å in accordance with the above theory.

It might be tempting to conclude that some sort of quinonoid electronic structure was present in the p-bromo-benzenesulphonyloxy- part of the molecule since the following

bonds have lengths somewhat shorter than standard values - S - C(12), C(13) - C(14), C(16) - C(17) and C(15) - Br, perhaps suggesting resonance of the form -



The electronegativity of the sulphur-oxygen double bond is well known. The linearity of the N-methyl-2:2-dimethylsulphonylvinylidineamine and N-methyl-2-methylsulphonyl-2-phenylsulphonylvinylidineamine molecules has been said to be due to the electron-attracting power of this bond acting as in the formulae above. (Wheatley, 1954., Bullough and Wheatley, 1957).

In pursuing this point the safest bond distance to examine is that between sulphur and bromine which has the smallest e.s.d. (<0.01Å). The calculated value for this distance is 6.44Å based on standard valency bond lengths. The experimental value - 6.31Å - is significantly shorter than this. If such an effect does exist, it is unlikely that it could cause a contraction of as much as 0.13Å, and it appears that the magnitude of this must be due to errors inherent in the data.

There is no sign of this phenomenon in the results of either Kartha (1964) or Gemmell and Sim (1964) mentioned earlier in this section, although it appears to be present to a much lesser extent in the molecule of 4,4'-dichlorodiphenyl sulphone. (Sime and Abrahams, 1960).

The intermolecular non-bonded distances listed in Table 14 all correspond to normal van der Waals' separations with the exception of those between O(4) and $O(1')_I$ and between O(3) and $O(1)_I$ which have values of 2.81Å and 2.87Å respectively, and which must represent hydrogen-bonding. This is confirmed by the fact that the average of the angles S - O(3) - $O(1)_I$, $C(9)_I$ - $O(1)_I$ - O(3), S - O(4) - $O(1')_I$ and $C(9)_I$ - $O(1')_I$ - O(4) is 103° - fairly close to the tetrahedral angle. Hargreaves (1957) found hydrogen bond lengths in the range 2.73Å to 2.82Å in zinc p-toluene sulphonate hexahydrate. This is in sensible agreement with the sulphur-oxygen double bond-hydroxyl hydrogen bond lengths quoted above.

The O(3) - S - O(4) bond angle of 114° is significantly greater than tetrahedral. This may well be due to van der Waals' repulsive forces operating between O(3) and O(4) which have a separation of only 2.42Å. This conforms to a general pattern in sulphonyl and related groups, the mean O - S - O angles in both zinc p-toluene sulphonate hexahydrate (Hargreaves, 1957) and potassium ethyl sulphate (Truter, 1958) being 113°.

TABLE 10

BROS.

Course of structure analysis and refinement

Operation	Atoms included	R(%)	$\Sigma w\Delta^2$
2D Patterson synthesis	-	-	-
3D " "	-	-	-
1st 3D Fourier Synthesis	Br+S+2(C)	41.4	-
2nd 3D " "	Br+S+17(C)+4(O)	27.2	-
3rd 3D " "	Br+S+17(C)+3(O)+$2(O)_{0.5}$	24.8	-
4th 3D " "	Br+S+17(C)+3(O)+$O_{0.6}$+$O_{0.4}$	23.1	-
5th 3D " "	Br+S+17(C)+3(O)+$O_{0.55}$+$O_{0.45}$	20.9	-
6th 3D " "	Br+S+17(C)+3(O)+$2(O)_{0.5}$	20.1	-
1st Least Squares Cycle (w_1)	Br+S+17(C)+3(O)+$2(O)_{0.5}$	19.5	1225
2nd " " "	"	18.4	1186
3rd " " "	"	15.9	906
4th " " "	"	14.1	730
5th " " "	"	13.4	662
6th " " "	"	13.1	635
7th " " "	"	12.9	620
8th Least Squares Cycle (W_2)	"	13.0	417
9th " " "	"	12.9	393

TABLE 11

BROS.

Atomic Coordinates

Atom	x/a	y/b	z/c
C(1)	0.5149	0.4307	0.2186
C(2)	0.7011	0.3530	0.1666
C(3)	0.6584	0.2407	0.0483
C(4)	0.5351	0.1692	0.0572
C(5)	0.3523	0.2486	0.1132
C(6)	0.1974	0.3103	0.0150
C(7)	0.2590	0.4079	-0.0068
C(8)	0.3631	0.4984	0.1238
C(9)	0.4206	0.3481	0.2418
C(10)	0.2597	0.1645	0.1394
C(11)	0.5763	0.5247	0.3525
C(12)	0.8198	0.7893	0.3964
C(13)	1.0083	0.7481	0.3809
C(14)	1.0827	0.8101	0.3434
C(15)	0.9715	0.9188	0.3141
C(16)	0.7836	0.9651	0.3352
C(17)	0.7077	0.9024	0.3764
O(1)	0.2564	0.4259	0.2984
O(1')	0.5677	0.2904	0.3390
O(2)	0.6549	0.6126	0.3308
O(3)	0.8779	0.6643	0.5518
O(4)	0.5613	0.7954	0.5111
S	0.7268	0.7162	0.4600
Br	1.0781	1.0024	0.2532

TABLE 12

BROS.

Intramolecular bonded distances (Å)

C(1) ... C(2)	1.57	C(9) ... O(1')	1.49
C(1) ... C(8)	1.55	C(11) ... O(2)	1.48
C(1) ... C(9)	1.51	C(12) ... S	1.72
C(1) ... C(11)	1.52	C(12) ... C(13)	1.38
C(2) ... C(3)	1.52	C(12) ... C(17)	1.43
C(3) ... C(4)	1.48	C(13) ... C(14)	1.30
C(4) ... C(5)	1.58	C(14) ... C(15)	1.42
C(5) ... C(6)	1.54	C(15) ... C(16)	1.40
C(5) ... C(9)	1.53	C(15) ... Br	1.87
C(5) ... C(10)	1.54	C(16) ... C(17)	1.34
C(6) ... C(7)	1.51	O(2) ... S	1.57
C(7) ... C(8)	1.57	O(3) ... S	1.43
C(9) ... O(1)	1.47	O(4) ... S	1.45

TABLE 13.

BROS.

Intramolecular non-bonded distances (Å)(<4Å)

C(1) ... C(7)	2.60	C(7) ... C(10)	3.88		
C(1) ... C(3)	2.58	C(7) ... C(9)	2.95		
C(1) ... C(4)	2.97	C(7) ... C(11)	3.91		
C(1) ... C(6)	2.97	C(7) ... O(1)	3.39		
C(1) ... C(5)	2.51	C(8) ... C(9)	2.50		
C(1) ... C(10)	3.87	C(8) ... C(11)	2.50		
C(1) ... O(2)	2.42	C(8) ... O(2)	2.83		
C(1) ... S	3.86	C(8) ... O(1)	2.84		
C(1) ... O(1)	2.40	C(8) ... O(1')	3.81		
C(1) ... O(1)'	2.43	C(9) ... C(10)	2.52		
C(2) ... C(7)	3.23	C(9) ... C(11)	2.43		
C(2) ... C(4)	2.54	C(9) ... O(2)	3.72		
C(2) ... C(6)	3.65	C(10) ... O(1)	2.97		
C(2) ... C(5)	2.99	C(10) ... O(1')	2.93		
C(2) ... C(8)	2.61	C(11) ... C(12)	3.91		
C(2) ... C(9)	2.52	C(11) ... O(3)	2.98		
C(2) ... C(11)	2.53	C(11) ... O(4)	3.06		
C(2) ... O(2)	2.95	C(11) ... S	2.56		
C(2) ... O(1)	3.79	C(11) ... O(1)	2.75		
C(2) ... O(1)'	2.87	C(11) ... O(1')	2.79		
C(3) ... C(7)	3.06	C(12) ... C(15)	2.73		
C(3) ... C(6)	3.19	C(12) ... C(16)	2.39		
C(3) ... C(5)	2.57	C(12) ... C(14)	2.32		
C(3) ... C(8)	3.21	C(12) ... O(2)	2.51		
C(3) ... C(10)	3.87	C(12) ... O(3)	2.59		
C(3) ... C(9)	2.94	C(12) ... O(4)	2.62		
C(3) ... C(11)	3.89	C(13) ... C(15)	2.37		
C(3) ... O(1)'	3.38	C(13) ... C(16)	2.78		
C(4) ... C(7)	3.18	C(13) ... C(17)	2.44		
C(4) ... C(6)	2.58	C(13) ... S	2.70		
C(4) ... C(8)	3.65	C(14) ... C(16)	2.44		
C(4) ... C(10)	2.53	C(14) ... Br	2.86		
C(4) ... C(9)	2.53	C(14) ... C(17)	2.76		
C(4) ... O(1)	3.85	C(14) ... S	3.90		
C(4) ... O(1)'	2.92	C(15) ... C(17)	2.37		
C(5) ... C(7)	2.57	C(16) ... Br	2.84		
C(5) ... C(8)	2.99	C(16) ... S	3.95		
C(5) ... C(11)	3.82	C(17) ... O(2)	3.45		
C(5) ... O(1)	2.48	C(17) ... O(3)	3.79		
C(5) ... O(1)'	2.47	C(17) ... O(4)	2.94		
C(6) ... C(8)	2.58	C(17) ... S	2.70		
C(6) ... C(10)	2.50	O(1) ... O(1')	2.41		
C(6) ... C(9)	2.50	O(2) ... O(3)	2.46		
C(6) ... O(1)	2.91	O(2) ... O(4)	2.47		
C(6) ... O(1)'	3.82	O(3) ... O(4)	2.42		

TABLE 14

BROS.

Intermolecular distances (Å) (<4Å)

O(4) ... $O(1')_I$	2.81	O(3) ... $O(3)_{VI}$	3.73
O(3) ... $O(1)_I$	2.87	O(4) ... $O(1)_I$	3.73
C(14) ... $O(4)_{II}$	3.40	C(12) ... Br_V	3.76
C(10) ... Br_{III}	3.46	C(6) ... $C(15)_{VII}$	3.76
C(16) ... $O(4)_{IV}$	3.55	C(9) ... $O(4)_I$	3.77
C(17) ... $O(4)_{IV}$	3.56	C(15) ... $C(17)_V$	3.78
C(11) ... $O(1)_I$	3.59	C(9) ... $O(3)_I$	3.78
C(10) ... $O(4)_I$	3.62	O(4) ... Br_V	3.79
C(10) ... $O(3)_I$	3.63	C(17) ... Br_V	3.80
C(16) ... $C(14)_V$	3.64	C(6) ... $C(14)_{VII}$	3.82
C(2) ... $O(3)_{VI}$	3.66	O(3) ... Br_V	3.83
C(11) ... $O(1')_I$	3.67	C(7) ... $C(7)_{VIII}$	3.84
C(13) ... $O(1)_{II}$	3.67	C(7) ... $O(2)_{VII}$	3.84
C(15) ... $C(16)_V$	3.67	C(15) ... $C(15)_V$	3.84
S ... $O(1')_I$	3.68	S ... BrV	3.94
S ... $O(1)_I$	3.70	C(8) ... $C(8)_{VII}$	3.99
C(13) ... $O(1')_{VI}$	3.71	C(7) ... $C(13)_{VII}$	3.99
O(3) ... $O(1')_I$	3.72	C(13) ... $O(4)_{II}$	3.99

The subscripts refer to the following positions:

I	-1 - x, -1 - y, 1 - z	V	-x, -y, 1 - z
II	x + 1, y, z	VI	-x, -1 - y, 1 - z
III	x - 1, y - 1, z	VII	-1 - x, -1 - y, -z
IV	-1 - x, -y, 1 - z	VIII	-1 - x, -1 - y, -z

TABLE 15

BROS.

Valency Angles

C(1)C(2)C(3)	113°	C(5)C(9)O(1)	111°
C(2)C(3)C(4)	116	C(5)C(9)O(1')	110
C(3)C(4)C(5)	115	O(1)C(9)O(1')	109
C(4)C(5)C(6)	112	C(1)C(11)O(2)	107
C(4)C(5)C(9)	109	C(11)O(2) S	114
C(4)C(5)C(10)	109	O(2) S C(12)	100
C(10)C(5)C(6)	109	O(2) S O(3)	110
C(10)C(5)C(9)	110	O(2) S O(4)	110
C(6)C(5)C(9)	109	O(3) S C(12)	111
C(5)C(6)C(7)	115	O(4) S C(12)	111
C(6)C(7)C(8)	114	O(3) S O(4)	114
C(7)C(8)C(1)	112	S C(12)C(13)	121
C(8)C(1)C(2)	113	S C(12)C(17)	118
C(8)C(1)C(9)	110	C(17)C(12)C(13)	120
C(8)C(1)C(11)	109	C(12)C(13)C(14)	120
C(2)C(1)C(9)	109	C(13)C(14)C(15)	121
C(2)C(1)C(11)	110	C(14)C(15)C(16)	120
C(9)C(1)C(11)	106	C(14)C(15) Br	120
C(1)C(9)C(5)	111	C(16)C(15) Br	120
C(1)C(9)O(1)	107	C(15)C(16)C(17)	119
C(1)C(9)O(1')	108	C(16)C(17)C(12)	119

TABLE 16

BROS.

Standard deviations of the final atomic coordinates (Å)

Atom	$\sigma(x)$	$\sigma(y)$	$\sigma(z)$
C(1)	0.018	0.017	0.018
C(2)	0.019	0.019	0.020
C(3)	0.023	0.020	0.023
C(4)	0.021	0.017	0.020
C(5)	0.017	0.016	0.019
C(6)	0.018	0.018	0.020
C(7)	0.021	0.017	0.021
C(8)	0.019	0.016	0.018
C(9)	0.018	0.015	0.017
C(10)	0.020	0.017	0.021
C(11)	0.022	0.017	0.021
C(12)	0.017	0.015	0.016
C(13)	0.020	0.017	0.023
C(14)	0.022	0.019	0.022
C(15)	0.021	0.017	0.023
C(16)	0.021	0.018	0.019
C(17)	0.021	0.018	0.018
O(1)	0.022	0.021	0.022
O(1')	0.029	0.024	0.026
O(2)	0.012	0.010	0.012
O(3)	0.015	0.012	0.013
O(4)	0.015	0.014	0.016
S	0.005	0.004	0.005
Br	0.003	0.002	0.003

TABLE 17

BROS.

Anisotropic temperature-factor parameters ($10^5 b_{ij}$).

Atom	b_{11}	b_{22}	b_{33}	b_{23}	b_{13}	b_{12}
C(1)	3753	1178	1144	-277	1340	-2268
C(2)	3104	1469	1648	516	1164	-1071
C(3)	5153	1289	2062	-307	2796	-1427
C(4)	3475	1040	1800	1113	1072	533
C(5)	2490	1156	1540	962	371	-1088
C(6)	2685	1574	1906	1316	459	-1748
C(7)	4961	1113	1764	946	437	-1674
C(8)	3941	1103	941	179	1009	-1809
C(9)	3362	858	923	356	-73	-1238
C(10)	4035	917	1893	223	860	-1549
C(11)	6490	1039	1659	401	491	-3207
C(12)	3146	868	1060	745	1637	-530
C(13)	3317	1085	2854	1404	456	-1459
C(14)	4329	1038	2111	720	2002	157
C(15)	5108	942	2293	198	268	-3291
C(16)	5047	1580	1525	1996	1590	-987
C(17)	4727	1403	1121	1183	1028	-1245
O(1)	2633	976	1066	221	1269	-984
O(1')	5029	1250	1321	929	-346	-1224
O(2)	5522	1200	1434	373	905	-3745
O(3)	5234	1644	1438	1242	332	-2228
O(4)	4486	1702	2451	414	2403	-1283
S	3780	1049	1031	162	865	-1910
Br	5388	1458	1668	679	1485	-2743

Table 18 BROS

Final observed and calculated values of the structure factors.

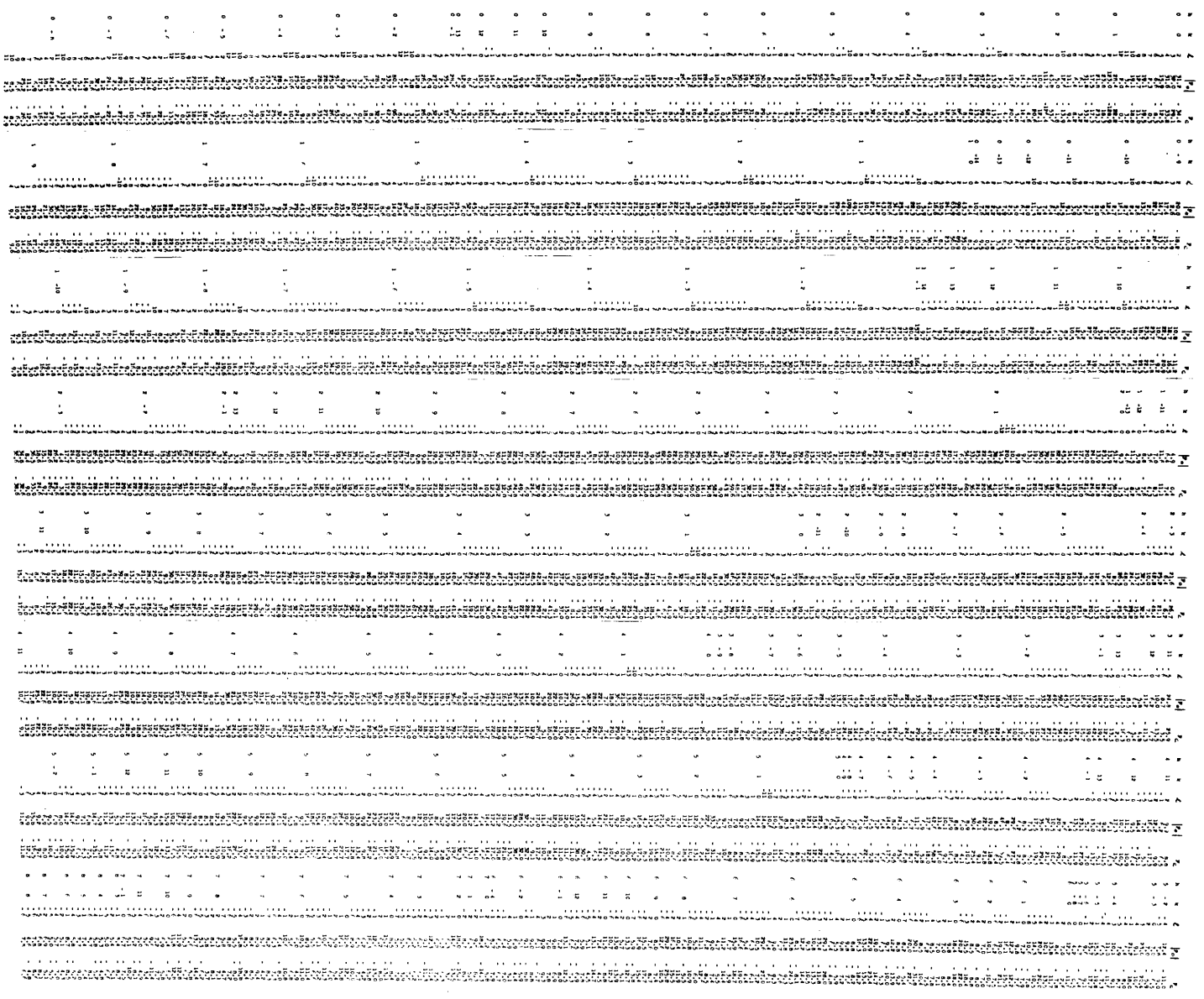


TABLE 19

BROS.

Deviations (Å) of atoms from mean planes

a) Plane defined by C(1)C(8)C(6)C(5)

Atom	Deviation	Atom	Deviation
C(1)	0.00	C(5)	0.00
C(8)	0.00	C(9)	-0.72
C(6)	0.00	C(7)	+0.45

b) Plane defined by C(1)C(2)C(4)C(5)

Atom	Deviation	Atom	Deviation
C(1)	-0.01	C(5)	+0.01
C(2)	+0.01	C(9)	+0.71
C(4)	-0.01	C(3)	-0.51

c) Plane defined by C(11)C(1)C(9)C(5)C(10)

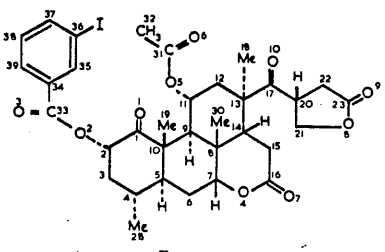
Atom	Deviation	Atom	Deviation
C(11)	0.00	C(2)	+1.32
C(1)	0.00	C(6)	-1.28
C(9)	-0.01	C(7)	-1.50
C(5)	0.00	C(8)	-1.29
C(10)	+0.01	O(1)	-1.21
C(4)	+1.30	O(1')	+1.21
C(3)	+1.54		

d) Plane defined by C(12)C(13)C(14)C(15)C(16)C(17)S Br

Atom	Deviation	Atom	Deviation
C(12)	-0.06	C(16)	+0.02
C(13)	-0.01	C(17)	0.00
C(14)	+0.03	S	+0.03
C(15)	0.00	Br	-0.01

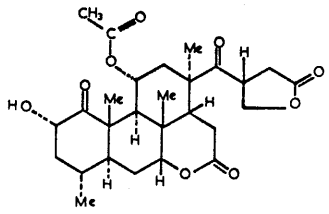
PART IV

THE STRUCTURAL AND STEREOCHEMICAL DETERMINATION OF SIMAROLIDE



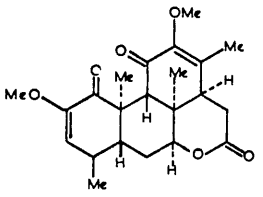
I

SIMAROLIDE M - IODOBENZOATE



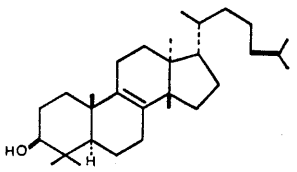
II

SIMAROLIDE



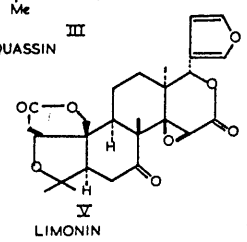
III

QUASSIN



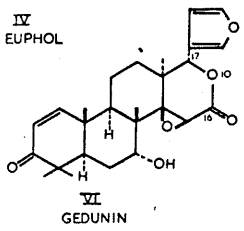
IV

EUPHOL



V

LIMONIN



VI

GEDUNIN

Fig. 21

4.(1). Introduction.

Simarolide is a bitter principle which has been isolated from the bark of a tree of the Simaruba amara family which grow in Brazil (Polonsky, 1959). Many compounds obtained from this family of trees have found application as drugs. They have been used as cures for dysentry, as febrifuges and as tonics.

Prior to this x-ray investigation not much was known about the structure of simarolide. Polonsky (1959) had found that there were no carbon-carbon double bonds and neither methoxyl or ethoxyl groups were present. She was able to prove the presence of the following functional groups -
(a) an acetoxyl group since alkaline hydrolysis furnished acetic acid,
(b) a hydroxyl group which was identified spectroscopically and by formation of the corresponding acetate,
(c) a γ-lactone which was shown to be present by infra-red measurements and by quantitative saponification with potassium hydroxide,
(d) a masked carbonyl group, which only displayed characteristic properties after prolonged alkaline hydrolysis.

She also concluded that the gross molecular formula was $(C_3H_4O)_9$.

The first derivative on which work was done was the m-iodobenzoate, obtained by esterifying the hydroxyl group of simarolide.

As will be explained later, it became necessary to attack the structural problem using another heavy atom derivative, and the 4-iodo-3-nitrobenzoate was supplied by Mme. Polonsky in this connection.

So as to be specific in identifying atoms in the course of the analysis, the final structure and absolute stereochemistry (I) and the conventional numbering system of simarolide m-iodobenzoate are shown in Fig. 21.

a) X-ray analysis of simarolide m-iodobenzoate.

4.(2). Experimental.

The usual photographs were taken using copper - K_α ($\lambda = 1.5418\text{Å}$) and molybdenum - K_α ($\lambda = 0.7107\text{Å}$) radiations. The unit cell parameters were established from precession photographs.

The intensity data were collected under the same experimental conditions as obtained in the analyses described earlier. Zero layer and equi-inclination upper-layer Weissenberg photographs were recorded by rotating the crystal about its unique b-axis. In this way reciprocal lattice nets hol, ----, h4l were registered.

The intensity values were reduced to $|F_o|$'s as in the case of 5-bromogriseofulvin (section 2.(2).) and then placed on the same scale by comparison with the first $|F_c|$ values.

In total, 1258, independent observable intensity estimations were performed.

The crystal density was found by the usual flotation technique using potassium iodide solutions and methylene chloride - chloroform mixtures.

4.(3). Crystal Data.

$C_{34}.H_{39}.O_{10}.I.$ $M = 734.6$

monoclinic $a = 13.81 \pm 0.08\text{Å}$

$b = 6.57 \pm 0.02\text{Å}$

$c = 20.16 \pm 0.07\text{Å}$

$\beta = 94^{\circ}27'$

Volume of the unit cell = $1,824\text{Å}^3$

for $z = 2$, D(Calculated) = 1.34 g./cc.

D(Observed) = 1.50 g./cc.

F(000) = 752

Linear absorption coefficient for x-rays ($\lambda = 1.5418\text{Å}$)

$\mu = 88.7 \text{ cm.}^{-1}$.

Systematically absent reflections: (oko) when $k = 2n + 1$

As in the case of 5-bromogriseofulvin it was decided to assign the crystals to space group $P2_1$ rather than to $P2_1/m$ since the molecule is optically active.

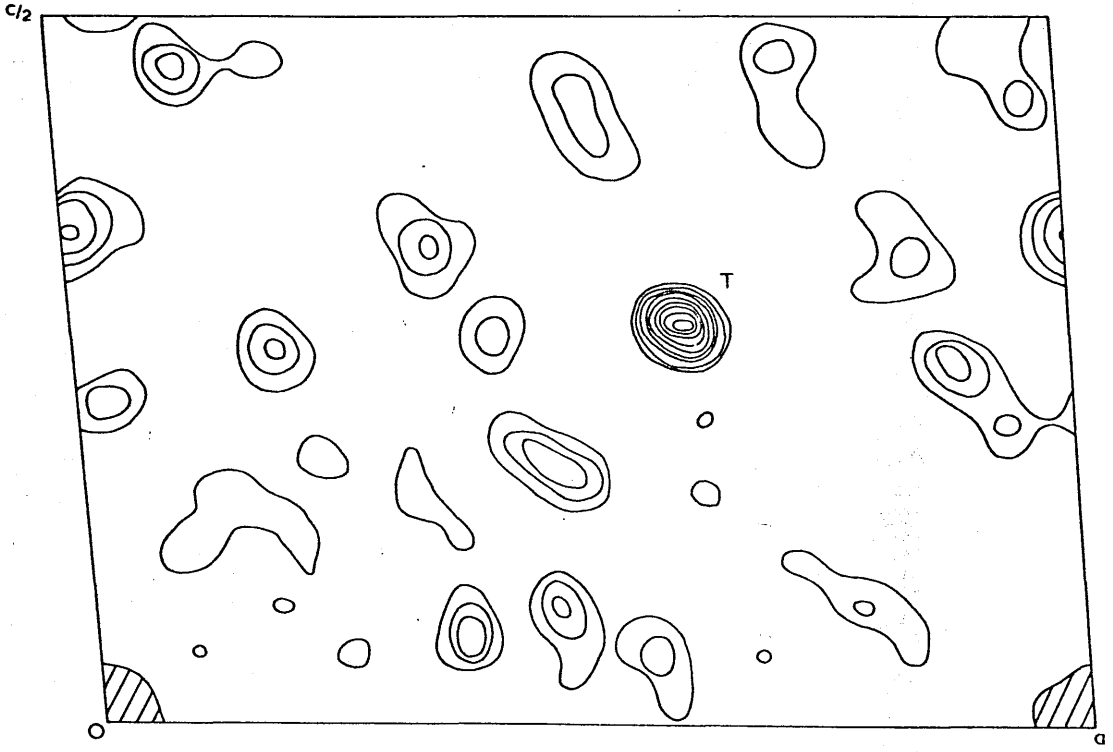


Fig. 22 Simarolide m-iodobenzoate.

hol Patterson projection. Contour scale arbitrary.

The discrepancy between the values for the calculated and observed densities will be discussed later.

4.(4). Location of the Heavy Atom Position.

As explained in section 2.(4)., the choice of origin along the screw axis in space group $P2_1$ is arbitrary and it is convenient to place it half way between the two iodine atoms.

The Patterson function for space group $P2_1$ is also given in section 2.(4). and, since there is only one heavy atom in the asymmetric unit on this occasion, there is only one peak to be located from the vector map in order to evaluate the iodine coordinates.

The hol Patterson projection was computed and the expected peak showed up at $u = 2x_I$, $w = 2z_I$. The maximum is marked T in the reproduction of the map in Fig. 22.

The iodine coordinates obtained were -

$x/a = 0.3067$ $y/b = 0.2500$ $z/c = 0.1423$

4.(5). Solution of the structure.

The value of $\underline{r}$ (see section 1.(2).) is 1.22. This factor indicated that there would be a good chance of a fairly low average phase angle error in the phasing calculation employing the iodine parameters alone.

An isotropic temperature factor of $\alpha = 3.0$ was assumed for this first calculation for which the overall R-factor was 44.1%. 1139 of these structure factors were reckoned to have phase angles sufficiently correctly determined so as to enable them to be employed as Fourier coefficients.

This map was computed as a series of equidistant sections through the unit cell parallel to (010).

It was only necessary to evaluate the electron density over one quarter of the unit cell volume. This is due to the fact that there are two equivalent positions in the unit cell and, in addition, due to the phase ambiguity in $P2_1$ (see section 2.(5).) there is a false mirror plane at $y = \frac{1}{4}$ and $y = \frac{3}{4}$. As soon as atoms off this plane are included in the phasing calculation, however, it is necessary to compute the Fourier series over half of the unit cell volume.

From the first Fourier map it appeared possible to pick out the m-iodobenzoate part of the structure. The distribution was, of course, very complicated due to the interfusion of true molecules and their 'ghost' mirror images and it is impossible to distinguish these. The important point is to choose a self-consistent set of atomic coordinates i.e. either all 'true' atoms or all 'ghost' atoms. It was easy to obtain such a set of atoms from the planar benzene ring system, but it was felt

dangerous to locate any atoms in the general molecular skeleton in case they did not belong to the same set as the benzene ring and substituent atoms. It was, nevertheless, possible to place two further atoms since they lie on the plane at $y = \frac{1}{2}$ and are not, thus, accompanied by their mirror images. These atoms later turned out to be C(4) and C(5).

The second structure factor calculation included the coordinates and α-values of 3.0 of the iodine atoms and 10 other atoms which were all, in the meantime, taken to be carbon atoms. The overall R-factor was 40.9% - a drop of 3.2%.

This map was most disappointing since the benzene ring adopted an irregular shape, showing that atoms had not been located properly. It was decided to omit the benzene ring atom which deviated furthest from its ideal position and also C(4) and the carbon atom of the ester grouping since both of these latter atoms had peaks extending rather far in the y-direction. However, using the criterion of relative peak heights of true and 'ghost' atoms, it was possible to settle the positions of five more atoms which later turned out to be C(9), C(11), C(12), C(13) and O(10) although, at this stage, it was impossible to distinguish between oxygen and carbon chemical types.

The coordinates and α-values of 3.0 for the known atoms were then used in a third structure factor calculation for which the overall R-factor was 40.0% - a disappointing drop of 0.9%.

From the third electron density map it became obvious that the benzene ring had previously been quite erroneously chosen since its shape at the proposed site was worse than ever. Two of these six atoms were then fitted into a proposed cyclic system and it was found possible to calculate the coordinates of 21 atoms in all. These atoms later transpired to be C(1), C(2), C(3), C(4), C(5), C(8), C(9), C(10), C(11), C(12), C(13), C(14), C(19), C(28), C(31), O(2), O(5), iodine, C(6) and C(7). The last two were originally thought to be benzene ring atoms. In addition, one position was chosen which later turned out not to be an atomic site at all. No distinction could yet be made between oxygen and carbon. It was decided to use the same uniform α-value of 3.0 in the next phasing calculation.

The discrepancy for this next round of structure factors was 36.8% - a decrease of 3.2%. The resultant Fourier map, however, was most disconcerting in that some of the peaks originally considered to be those of 'ghost' atoms were larger than those of supposed true atoms,

indicating that correct x- and z- but wrong y-coordinates had been assigned to some atoms.

The only safe procedure appeared to be to insert the atoms and direct substituents of only one ring in the next structure factor computation and critically examine the consequent electron density map for a self-consistent ring system taking due account of molecular geometry and dimensions. The atoms so employed were C(8), C(9), C(11), C(12), C(13), C(14), C(31) and O(5). Iodine and O(2) both lay on the plane of false symmetry and were also used in the calculation. α was once more 3.0. This discrepancy rose as expected, the value being 41.2%.

Using the more reliable of these structure factors, an electron-density map was evaluated and drawn up. There was still no indication of the benzene ring and the pseudo-symmetric effect was very marked. Because of this latter disadvantage, it was decided to introduce a third chemical type into the phasing calculations. This was done by using the coordinates of both atoms and mirror images assigning to both scattering factors equal to half of that of carbon. This procedure has a dual benefit. Firstly, it does not bias the Fourier distribution in favour of one atom rather than its mirror image and, secondly, it helps to clear up the spurious electron density on the map.

The coordinates of the ten atoms used in the previous cycle were recalculated. These atoms were employed with full-scale carbon scattering factors as were C(1), C(4) C(6), C(7), C(19), C(20), C(28) and O(7) which all lay on or very near the plane at $y = \frac{1}{4}$. The coordinates of the following atoms, (x y z), with those of their mirror images, (x, $\frac{1}{2}$-y, z), were used with half-scale carbon scattering factors - C(5), C(10), C(15), C(16), C(22), C(32), O(4) and O(6).

When the structure factors were computed, the R-factor, summed over all terms, was 35.4% - a decrease of 5.8%. The Fourier map which was then computed indicated five additional atoms with their 'ghost' peaks. They were C(2), C(3), C(18), C(33) and O(3). In addition, C(1) now appeared very distended in the y-direction, and it was decided to place it off the mirror plane, and comprise it with its mirror image in the next calculation. Examination of the half-weight peak heights showed that of the eight atoms so employed in the previous cycle, only C(5), C(16) and C(22) could not be at least tentatively placed on one side or the other of the mirror plane. To be safe, however, only C(32) and O(6) were employed as full-weight atoms in the next stage of the analysis.

The discrepancy for the seventh structure factor calculation fell by 1.9% to 33.5%. Since the benzene ring had still to be located it was decided to examine F_o and $(F_o - F_c)$ syntheses projected down the unique axis in an attempt to obtain a solution. It was found that the benzene ring could be fitted into the structure on the opposite side of the iodine atom from that used originally. Four other new atoms - C(17), C(20), O(1) and O(10) - were located from the projection maps. C(18) was omitted at this stage since it appeared to be possibly not genuine. The $(F_o - F_c)$ map was also used to indicate coordinate shifts and the α-value for iodine was increased to 3.8.

In the subsequent structure factor calculations O(2), O(5) and O(6) were inserted as oxygen atoms and it was, of course, no longer necessary to employ half-weight atoms since it was decided to attempt refinement of atomic positions by two-dimensional difference maps. After five such cycles the discrepancy had fallen from 37.1% to 31.4%.

Previous values of y-coordinates were then used with the exception of those of the atoms of the benzene ring which were evaluated from the tilt of the ring. The only atom which still required to be used along with its mirror image was C(22). When this cycle of three-dimensional structure factors had been calculated, the R-factor was 28.9% - a decrease of 4.6% from the seventh cycle.

Two further rounds of three-dimensional F_o and $(F_o - F_c)$ syntheses failed to reveal any further atomic positions. The structure, indeed, appeared to be of a polymeric nature since bands of electron density appeared to be continuing indefinitely in the Fourier map. It was, of course, known that the compound was definitely not a macro-molecule. The difference maps were used to indicate coordinate adjustments and reduced the overall discrepancy to 26.9%.

One of the difficulties of solving this problem was that the crystals were undoubtedly solvated. Polonsky (1959) reported that simarolide recrystallised from various solvents appeared to partially melt about 180°C. and then completely melt at about 260°C. The first transition could be due to loss of solvent molecules. This is obviously the cause of the discrepancy between measured and calculated densities. This disparity could account for a solvent molecule of molecular weight up to 110. With this in view, a mass spectrum was run, but it was discovered that, by this time, all the solvent of crystallisation had evaporated, so no definite conclusion could be obtained about the nature of the solvent by this means. From the crystallographic point of view the solvent was hard to detect presumably due to the fact that the site occupancy was not 100% and also the

temperature factors associated with the constituent atoms would be expected to be very high.

At this stage Mme. Polonsky provided crystals of simarolide 4-iodo-3-nitrobenzoate, and so the m-iodobenzoate work was temporarily shelved.

b). X-ray analysis of simarolide 4-iodo-3-nitrobenzoate.

4.(6). Experimental.

The experimental conditions and methods were the same as those described in section 4.(2)., except that the data were collected by rotation about the c-axis and, in all, the intensities of 1808 reflections were estimated from the reciprocal lattice nets hko, ----, hk5.

4.(7). Crystal Data.

$C_{34}H_{38}O_{12}NI$ M = 779.6

Orthorhombic

a = 20.73 ± 0.06Å

b = 26.72 ± 0.07Å

c = 6.53 ± 0.02Å

Volume of the unit cell = 3,627Å^3

for z = 4, D(Calculated) = 1.43 g./cc.

D(Observed) = 1.53 g./cc.

F(000) = 1,592

Linear absorption coefficient for x-rays (λ = 1.5418Å)

μ = 76.1 cm.$^{-1}$.

Systematically absent reflections:

(hoo) when $h = 2n + 1$

(oko) when $k = 2n + 1$

This indicates that the space group must be $P2_12_12$.

The discrepancy between calculated and observed density values is again noticeable, suggesting that these crystals may also be solvated, as seems to be characteristic of crystals of simarolide and its derivatives.

4.(8). Location of the Heavy Atom Position.

The expression for the Patterson function for a crystal belonging to the orthorhombic system is -

$$P(uvw) = \frac{8}{V_c} \sum_{o}^{\infty} \sum_{o}^{\infty} \sum_{o}^{\infty} |F(hkl)|^2 \cos 2\pi hu \cos 2\pi kv \cos 2\pi lw$$

and this can simply be reduced to two-dimensional expressions.

The heavy atom vectors expected in space group $P2_12_12$ where $z = 4$ and there is one heavy atom per asymmetric unit are tabulated below.

-	2x, 2y, 0	$\frac{1}{2}$, $\frac{1}{2}$-2y, -2z	$\frac{1}{2}$-2x, $\frac{1}{2}$, -2z
2x, 2y, 0	-	$\frac{1}{2}$+2x, $\frac{1}{2}$, -2z	$\frac{1}{2}$, $\frac{1}{2}$+2y, -2z
$\frac{1}{2}$, $\frac{1}{2}$-2y, -2z	$\frac{1}{2}$+2x, $\frac{1}{2}$, -2z	-	2x, -2y, 0
$\frac{1}{2}$-2x, $\frac{1}{2}$, -2z	$\frac{1}{2}$, $\frac{1}{2}$+2y, -2z	-2x, 2y, 0	-

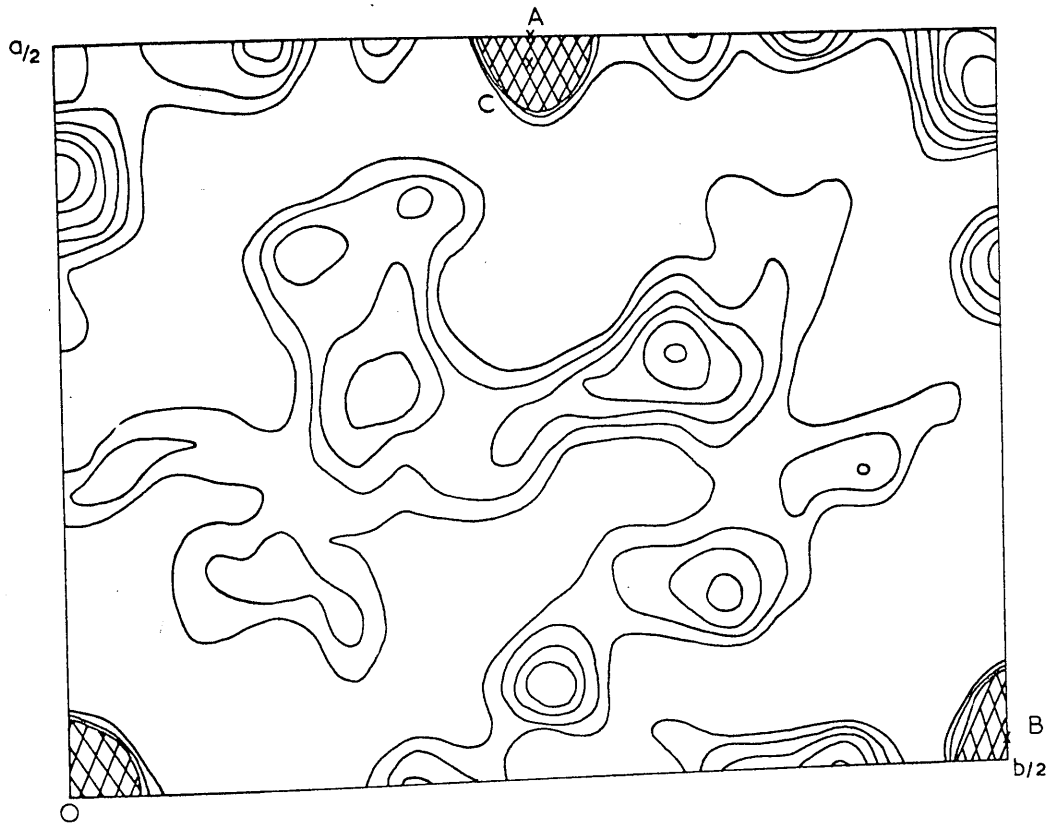


Fig. 23 Simarolide 4-iodo-3-nitrobenzoate.

hko Patterson projection. Contour scale arbitrary. Origin and major peak criss-crossed.

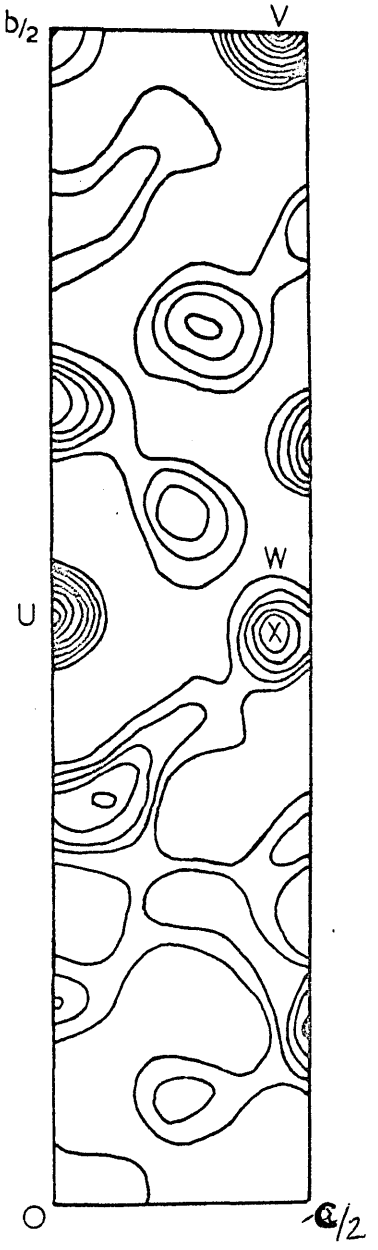


Fig. 24 Simarolide 4-iodo-3-nitrobenzoate.

okl Patterson projection. Contour scale arbitrary. Origin peak contours omitted.

The two-dimensional Patterson functions, P(uv) and P(vw) were computed and are shown in Figs. 23 and 24 respectively. Due to symmetry considerations it was only necessary to evaluate the syntheses over one quarter of the unit cell area.

The okl Patterson map (Fig. 24) is expected to have three predominant vectors - two in the special positions $(2y_I, 0)$ and $(\frac{1}{2}, 2z_I)$ and one in the general position $(\frac{1}{2} + 2y_I, 2z_I)$. They were all clearly resolved and are marked U, V and W respectively on the map.

The principal peaks expected in the hko Patterson map (Fig. 23) are $(\frac{1}{2}, \frac{1}{2} + 2y_I)$ and $(\frac{1}{2} + 2x_I, \frac{1}{2})$ in special positions and $(2x_I, 2y_I)$ in a general position. They were not so well resolved in this map, but are indicated by A, B and C. Only the x-coordinate for iodine was accepted from this distribution.

The iodine coordinates were calculated as

$x/a = 0.2386$ $\quad y/b = 0.1278$ $\quad z/c = 0.2013$

4.(9). Solution of the Structure.

These iodine coordinates and an isotropic temperature factor of $\mathcal{A}=4.0$ were used in the first structure-factor calculation for which the overall R-value was 38.8%.

Using 1704 of these terms a first three-dimensional Fourier map was computed in sections parallel to (001). All of the atoms with the exception of C(22), C(23), C(32), O(5), O(9), O(11) and O(12) were clearly resolved and their coordinates calculated. The derivative provided had originally been designated the 4-iodo-2-nitrobenzoate and since a peak appeared as if bonded to C(35) it was taken as the nitrogen atom. It was decided to proceed to a second phasing calculation using an α-value of 3.0 for atoms other than iodine, which was kept at 4.0.

The discrepancy summed over all terms in this cycle was 26.2% - a drop of 12.6%.

1763 of the structure factors were employed as Fourier coefficients in the second electron density calculation, and from the resulting map, all atoms except O(11) and O(12) were distinct. The nitrogen peak was very small and another equally strong peak showed up as if bonded to C(36). This was the first indication that the derivative might be the 4-iodo-3-nitrobenzoate. It was thought wise to omit the nitrogen atom from the next structure factor calculation. At this stage there was no suggestion of a possible site for the solvent molecule although there was a sizeable region of empty space in the electron-density distribution.

The next round of structure factors had an overall discrepancy of 22.3% - a drop of 3.9% and 1753 of them were adjudged suitable for inclusion in a third Fourier calculation. From this map it became clear that the nitro-group was attached to C(36) and was so inserted. A possible solvent molecule - acetone - was detected in the unit cell and this finding was confirmed by measurements on the mass spectrometer.

It was decided to compute structure factors for the hko zone including each of the solvent atoms singly and together in order to deduce if their positions were reliable. As mentioned in section 4.(5). the difficulty in detecting a non-hydrogen-bonded molecule of solvent of crystallisation is associated with the possibly incomplete site occupancy and the high values obtaining for temperature parameters. None of these calculations led to particularly conclusive results. Nevertheless, four tentative atomic positions were assigned.

A full three-dimensional structure factor calculation was performed and the overall R-factor was, disappointingly, 22.4% - an increase of 0.1% from the previous cycle.

1744 of these terms were employed in the computation of a difference Fourier synthesis. The usual coordinate shifts and temperature factor adjustments were made, but the value of R for the new structure factors dropped to only 22.1% - a decrease of 0.3%.

1770 of these structure factors were then used in the evaluation of F_o and F_c maps and the customary back-shift corrections were applied. It was noticed that the solvent molecule atomic peaks were very small and indistinct. It was suspected that perhaps the solvent molecules were disordered, and, with this in mind, it was decided to use very high α-values of 8.0 for these atoms in order to spread the electron density over a larger volume. It was thought that this would perhaps facilitate refinement after which more accurate sites for the solvent atoms might be found.

However, when the structure factors were computed, it was discovered that the discrepancy remained at 22.1%. Recalculation of the structure factors omitting the solvent molecule reduced the R-factor to 21.6%. These are the structure factors listed in Table 30.

It was then decided to postpone refinement of this structure till better and faster computing facilities were available when least squares procedure could be adopted.

In all the simarolide structure-factor calculations the theoretical scattering factors used were those of Berghius et al. (1955) for carbon, nitrogen and oxygen and the Thomas-Fermi (1935) values for iodine.

4.(10). Absolute configuration.

Intensities on the equi-inclination upper-layer Weissenberg photographs were examined for evidence of anomalous dispersion, and about a dozen pairs of reflections were picked out which should have had equal intensity had there been no anomalous scattering.

The indexing and choice of coordinate axes were carefully settled as explained in section 1.(4).

The particular enantiomorph present was then determined by comparing the values of $|F(hkl)|^2$ and $|F(\bar{h}\bar{k}\bar{l})|^2$ calculated on the basis of the anomalous scattering of the iodine atom with the values of $I(hkl)$ and $I(\bar{h}\bar{k}\bar{l})$.

If the differences between the $|F|^2$ values are in the same sense as the differences between the I values, then the enantiomorph used in the calculation is that actually present in the crystal. If they are in the opposite sense, however, the mirror image of the form used in the calculation is the true enantiomorph.

For iodine the dispersion corrections are:-

$\Delta f' = -1.1$ when $\sin\theta/\lambda = 0$

$= -1.3$ when $\sin\theta/\lambda = 0.6$

$\Delta f'' = 7.2$ when $\sin\theta/\lambda = 0$

$= 6.9$ when $\sin\theta/\lambda = 0.4$

$= 6.7$ when $\sin\theta/\lambda = 0.6$

(International Tables for Crystallography, Vol. III 1962a).

A typical calculation is shown for the (612) and $(\bar{6}\bar{1}\bar{2})$ reflections ($\sin\theta = 0.3256$) -

rel. I(612) = 786 > rel. I$(\bar{6}\bar{1}\bar{2})$ = 348

$A_{Total} = -22.48$ $B_{Total} = -23.85$

$A_{Iodine} = 25.44$ $B_{Iodine} = -45.39$

$$F_I^{anom.} = F_I^o + \frac{\Delta f'}{f_o} F_I^o + i \frac{\Delta f''}{f_o} F_I^o$$

a). Real correction term.

$$\frac{\Delta f'}{f_o} F_I^o = \frac{-1.1}{42} F_I^o = -0.03 F_I^o$$

This affects (612) and $(\bar{6}\bar{1}\bar{2})$ in the same way adding to the structure factor.

$$\frac{\Delta f'}{f_o} F_I^o = -0.03(25.44 \mp i.45.39)$$

$$= -0.76 \pm i.1.36$$

$$A = -22.48 - 0.76 = -23.24$$

$$B = \mp 23.85 \pm 1.36 = \mp 22.49$$

b). Imaginary correction term.

$$i \frac{\Delta f''}{f_o} F_I^o = i \frac{7.1}{42} F_I^o = i.(0.17) F_I^o$$

This term causes correction from Friedel's Law

$$i \frac{\Delta f''}{f_o} F_I^o = i.(0.17)(25.44 \mp i.45.39)$$

$$= 4.32i \pm 7.72$$

For (612) reflection -

$$\left.\begin{aligned} A &= -23.24 + 7.72 = -15.52 \\ B &= -22.49 + 4.32 = 18.17 \end{aligned}\right\} \quad (|F(612)|)^2 = 571$$

For $(\bar{6}\bar{1}\bar{2})$ reflection -

$$\left.\begin{aligned} A &= -23.24 - 7.72 = -30.96 \\ B &= 22.49 + 4.32 = 26.81 \end{aligned}\right\} \quad (|F(\bar{6}\bar{1}\bar{2})|)^2 = 1678$$

The differences between the $|F|^2$ and the I values are of opposite sense which means that the model chosen is the mirror image of the absolute configuration.

The other results are listed below and in every case this pattern was observed and the absolute stereochemistry was thus proved to be as in Fig. 21. (I).

Reflection	hkl		$\bar{h}\bar{k}\bar{l}$	
	rel. I_o	$\|F_c\|^2$	rel. I_o	$\|F_c\|^2$
511	80	1574	545	354
621	20	463	99	232
831	90	620	10	785
10,3,1	70	765	< 10	1109
2,21,1	80	310	40	543
922	1044	4339	928	5485
282	1965	2780	786	6094
623	30	59	70	3
2,12,3	630	896	378	1588
714	411	524	222	824
754	411	874	274	1087
315	80	110	129	74

c). Completion of structure analysis of simarolide. m-iodobenzoate.

4.(11). Solution of the Structure (contd.).

Having solved the gross molecular structure with the orthorhombic crystals it was decided to revert to a study of the m-iodobenzoate.

The remaining atoms were inserted and also two atoms of a possible solvent molecule which appeared to be rather like acetone although, as mentioned earlier, no mass spectrum evidence of this was obtained. Density considerations indicated that the solvent would have to have a molecular weight of about 110 which could be accounted for by two acetone molecules.

A set of structure factors was then computed and the overall discrepancy dropped by 1% to 25.9%.

1206 of these terms were used in the evaluation of an electron density map, in which the two solvent molecule atoms appeared as fairly low peaks, indicating the requirement of a larger temperature factor. Two other atoms, which were rather poorly resolved, were picked out to give one acetone molecule. The improved coordinates of the other atoms were calculated and the α-value for iodine increased to 4.8.

The discrepancy for the following phasing calculation was 24.7% - a decrease of 1.2%. Of these structure factors,

1204 were utilised in the computation of F_o and F_c syntheses. There was still no indication of the position of a second acetone molecule. The usual adjustments were made in coordinates and temperature factors and the new parameters were used in a further structure factor calculation for which the R-factor was 24.1% - a decrease of 0.6%. These are shown in Table 31.

Using 1218 of these terms an F_o map was computed over the region where the solvent molecules were presumed to be. However, not only was there no sign of a second molecule, but it became a matter of conjecture whether acetone was the solvent included at all. As in the case of the orthorhombic form, a set of structure factors was evaluated omitting the four solvent molecule atoms and the discrepancy rose by 0.5% to 24.6%. This proves that at least some of the atoms chosen for the solvent must be genuine.

This is as far as this analysis has reached, and, once more, least squares refinement with the faster computer is envisaged.

The course of these two analyses is shown in Tables 28 and 29.

4.(12). Results.

The latest atomic coordinates and temperature factors, α, for the 4-iodo-3-nitrobenzoate and the m-iodobenzoate of simarolide are listed in Tables 20 and 26 respectively. The former set of coordinates actually correspond to the mirror image of the true structure. The coordinates of four atoms of the possible acetone molecules are shown in each case.

From these coordinates were calculated various molecular parameters. Tables 21, 22, and 23 give a list of comparative and mean figures for bond lengths, bond angles and some of the intramolecular non-bonded distances. O refers to the orthorhombic crystals and M to the monoclinic ones.

A measure of the accuracy of these parameters may be found by comparing results for corresponding bond lengths and angles in the two independent crystal structures. The root-mean-square deviation of a bond length is about 0.096Å and of a bond angle, 7.1°. Since there are two independent measurements of each of the parameters, reasonable values for the estimated standard deviations of the averaged dimensions listed in Tables 21-23 can be obtained by division of the root-mean-square deviation by $\sqrt{2}$. This gives an e.s.d. of 0.07Å for a mean bond length and of 5° for a mean bond angle.

The various intermolecular non-bonded distances less than 4Å are shown in Tables 24 and 27 for the orthorhombic and monoclinic crystal structures respectively.

Some mean plane calculations were performed using the method of Schomaker et al. (1959). The deviations of the atoms from these planes are shown in Table 25 for simarolide 4-iodo-3-nitrobenzoate.

The latest values of $|F_o|$, $|F_c|$ and α for both structures are listed in Tables 30 and 31 respectively. These tables include only observed terms.

Using the latest structure factors in both cases three-dimensional Fourier maps were computed.

For the 4-iodo-3-nitrobenzoate the electron density distribution is portrayed in Fig. 25 by means of superimposed contour sections drawn parallel to (001). The possible acetone molecule is not shown. The corresponding atomic arrangement of the molecule is shown in Fig. 26. The packing of these molecules as viewed in projection down the c- and b-axes are drawn in Figs. 27 and 28.

The electron-density distribution of the m-iodobenzoate is shown in Fig. 29 by means of superimposed contour sections drawn parallel to (010). The corresponding molecular arrangement and packing diagram are portrayed in Figs. 30 and 31 respectively. Again the solvent molecule is not shown.

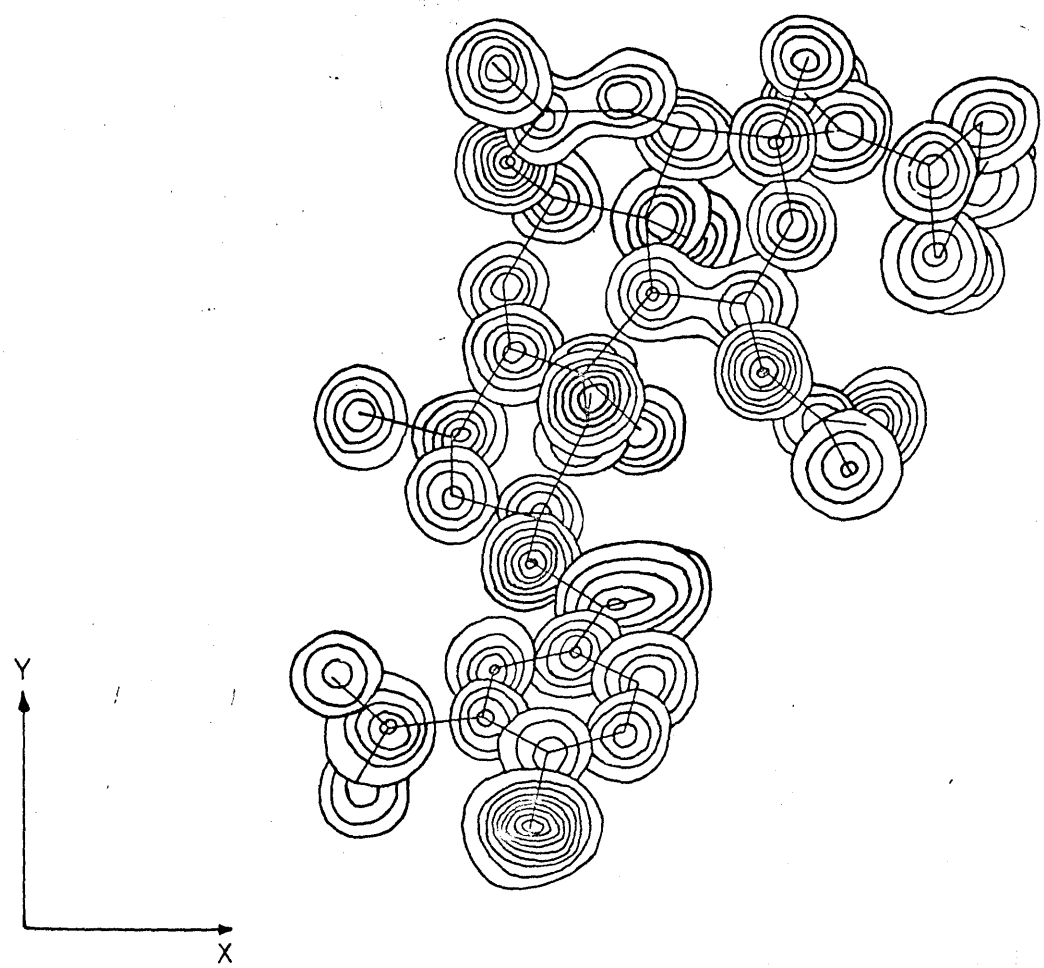


Fig. 25 Simarolide 4-iodo-3-nitrobenzoate.

Latest superimposed contour section electron density map drawn parallel to (001). All contour intervals at 1e/Å^3 except for iodine which is at 4e/Å^3.

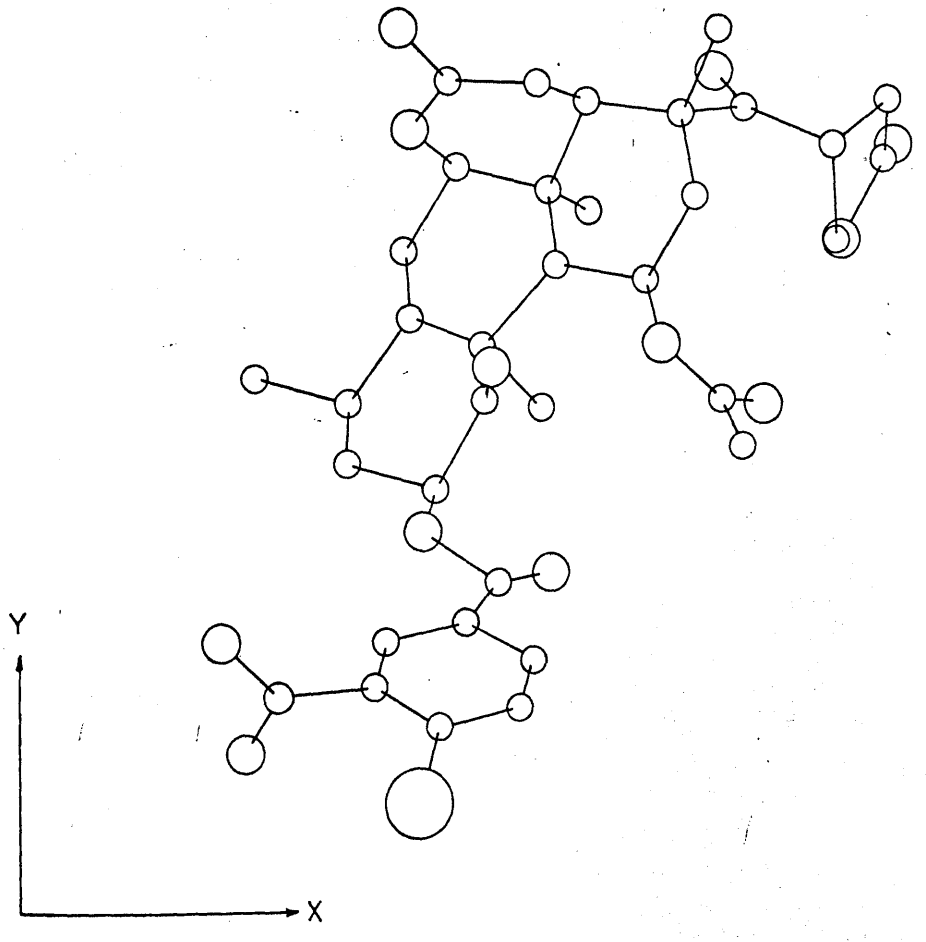


Fig. 26 Simarolide 4-iodo-3-nitrobenzoate.

Atomic arrangement corresponding to Fig. 25.

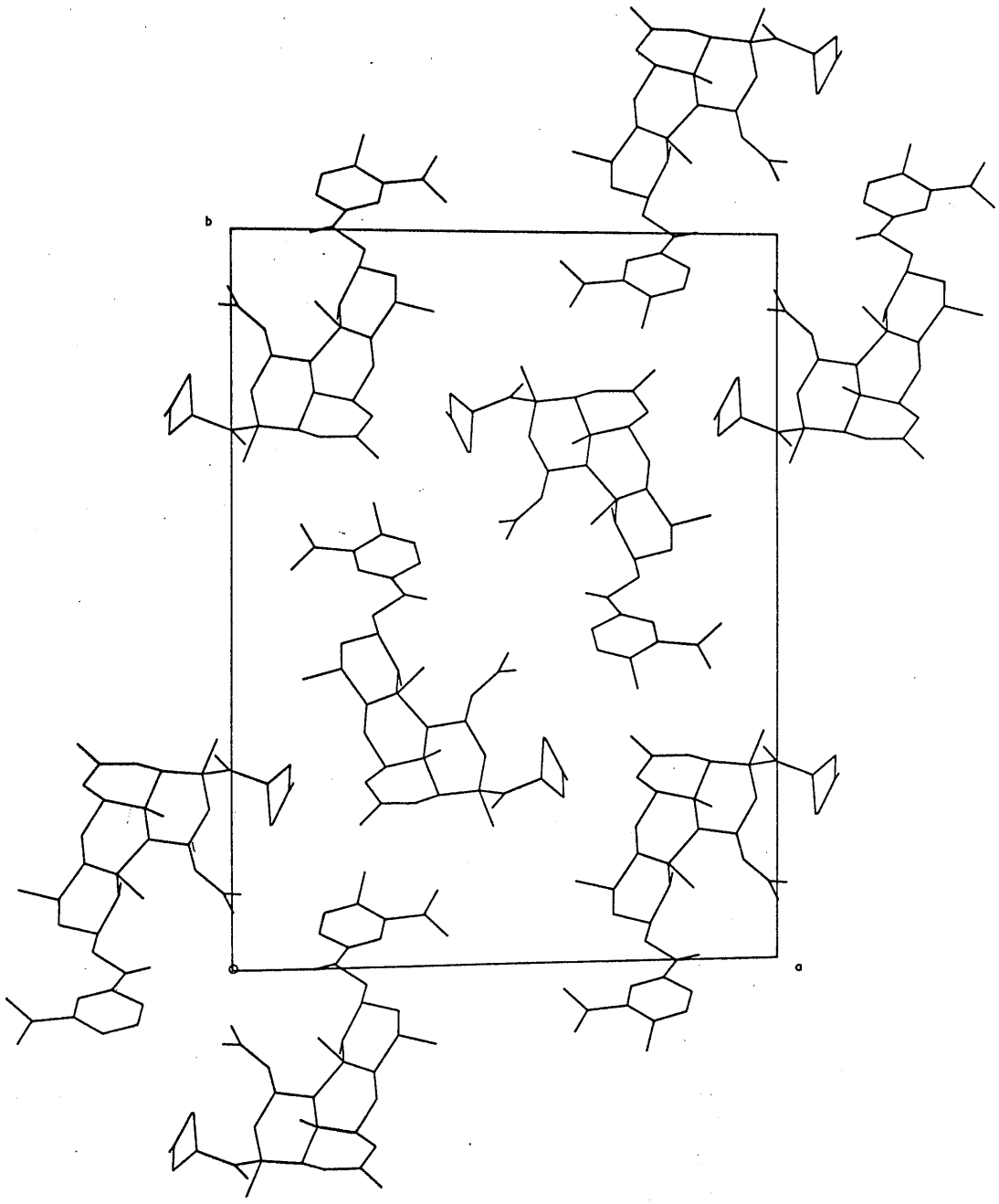


Fig. 27 Simarolide 4-iodo-3-nitrobenzoate.

Packing diagram as viewed down the c-axis.

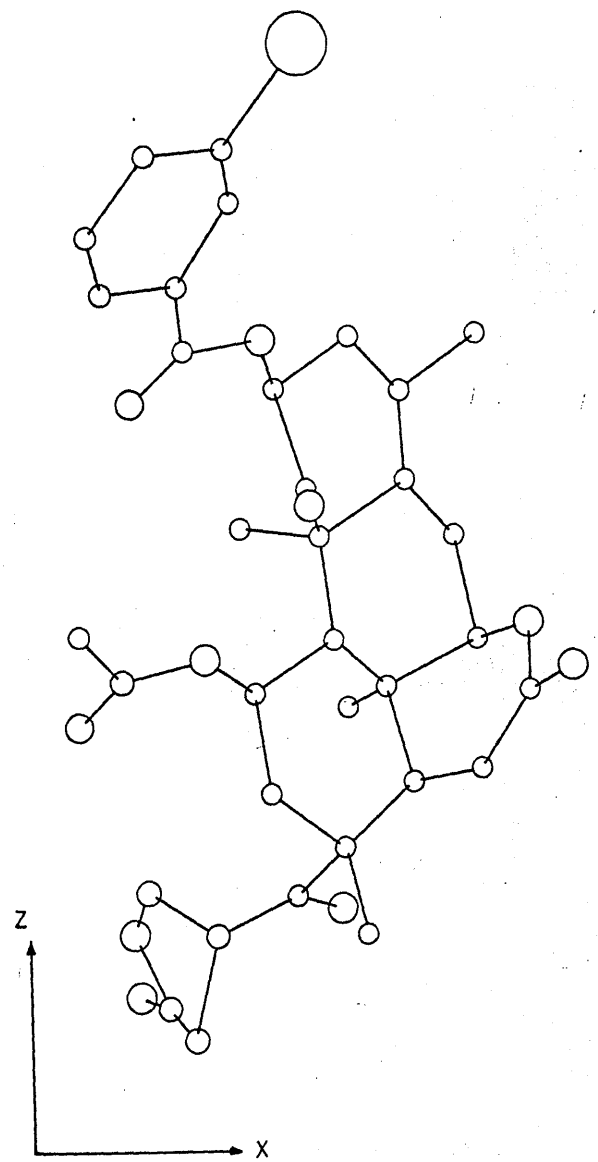


Fig. 30 Simarolide m-iodobenzoate.

Atomic arrangement corresponding to Fig. 29.

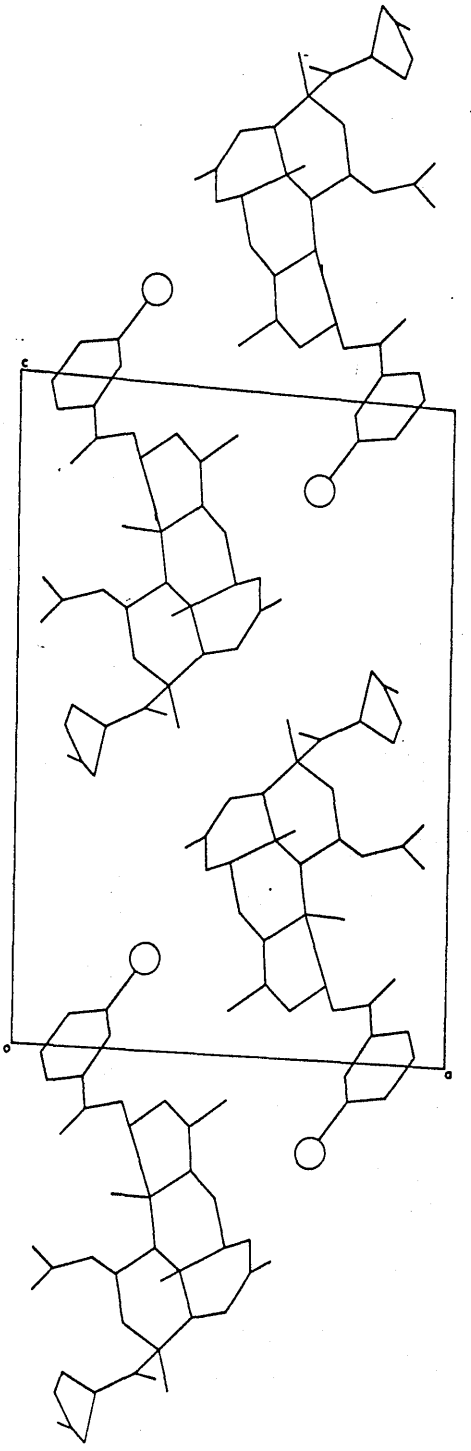


Fig. 31 Simarolide m-iodobenzoate.

Packing diagram as viewed down the b-axis.

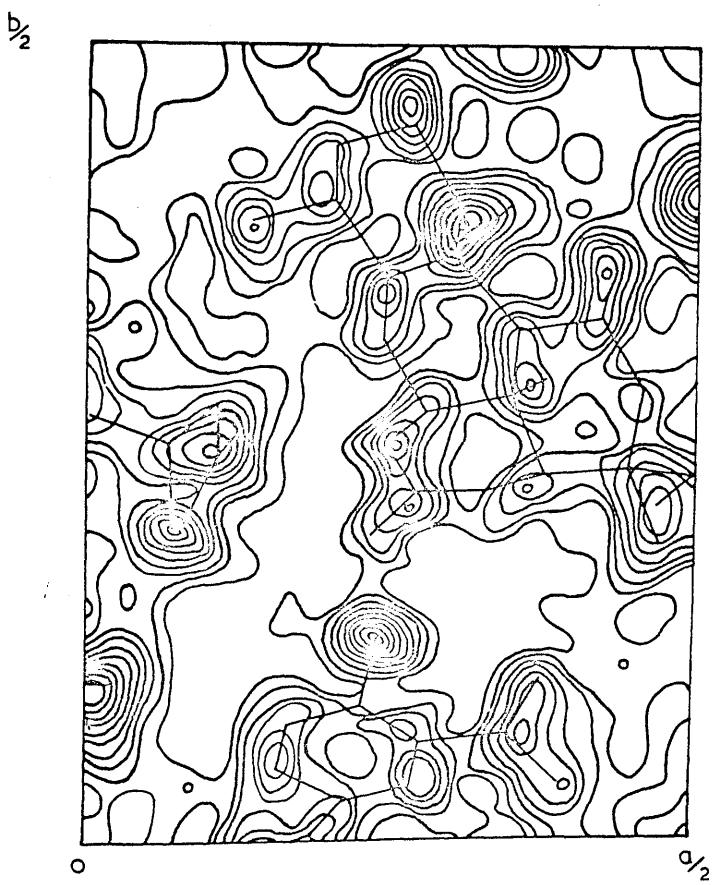


Fig. 32 Simarolide 4-iodo-3-nitrobenzoate.

Latest Fourier projection on (001) with superimposed molecular skeleton. All contour intervals at 1e/Å^3 except for iodine which is at 5e/Å^3.

As discussed in section 2.(8)., the electron density distribution is much more dependent on light atom positions in non-centrosymmetrical structures than in centrosymmetric cases. The projection of the 4-iodo-3-nitrobenzoate down the c-axis is centric and the molecular framework is shown superimposed on this map in Fig. 32. There is a reasonable agreement between atomic sites and peak maxima. The position of the postulated solvent molecule, the atomic coordinates of which were not used in the computation of this map, is in the top left hand and bottom right hand corner.

4.(13). Discussion.

The overall structure and absolute stereochemistry of simarolide are shown in Fig. 21. (II).

Another bitter principle from the Simaruba amara is quassin (III) whose structure and relative stereochemistry have recently been worked out by chemical and spectroscopic methods. (Valenta et al., 1962). It is interesting confirmation of the simarolide results, that the same relative stereochemistry is present at all seven common asymmetric centres.

Bredenberg (1964) has suggested that a simple biogenetic relationship exists between compounds of the quassin type and those of the limonin (IV) type (Arnott et al., 1961).

Simarolide, like limonin and gedunin (VI) (Sutherland et al., 1962) is evidently another triterpenoid compound of the euphol (V) type (Barton et al., 1954) in which the four carbon atoms at the end of the side chain have been removed and C(20) - C(23) have formed a saturated γ-lactone. Scission of the C(16) - O(10) bond in gedunin and the recyclisation of C(16) to O(4) would account for the δ - lactone and the C(17) carbonyl group in simarolide.

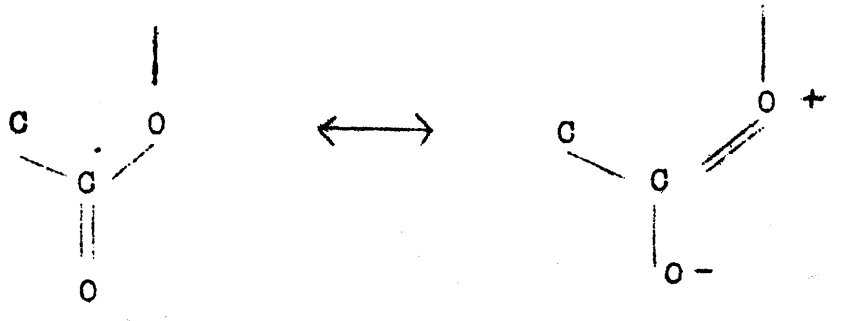
Since the two simarolide structures have not undergone thorough refinement and standard deviation values are high it follows that not much significance can be placed on individual bond lengths and angles and conclusions can only be drawn when it is possible to evaluate a truly representative average value for a parameter.

The following table summarises the bond lengths which are in sensible agreement with those of 5-bromogriseofulvin -

Bond	Simarolide	5-Bromogriseofulvin
sp^3-carbon-sp^3-carbon	1.54Å	1.54Å
sp^2-carbon-sp^3-carbon	1.51Å	1.49Å
Benzene carbon-carbon	1.37Å	1.40Å
sp^2-carbon-oxygen double	1.23Å	1.23Å

The carbon-oxygen single bonds are of two sharply contrasted types. Four of these are adjacent to carbonyl groups and have an average length of 1.38Å. The mean value

for the other four bonds is 1.48Å. This is a significant difference and shows that in ester and lactone groupings, as in carboxylic acids, there must be a considerable contribution from the charged resonance structure shown below -



Similar results have been obtained in other analyses. In bromodihydroisophoto-α-santonic lactone acetate (Asher, 1963) the respective values are 1.35Å and 1.47Å and in α-bromopicrotoxinin (Craven, 1962) they are 1.37Å and 1.47Å.

The average value of the aromatic carbon-iodine bond distance is 2.03Å which is in agreement with 2.10Å for the corresponding bond in picryl iodide (Huse and Powell, 1940).

The mean value of the nitrogen-oxygen bond, in the 4-iodo-3-nitrobenzoate, 1.26Å, is in accord with 1.21Å for m-dinitrobenzene (Trotter, 1961).

There is only one aromatic carbon-nitrogen bond in the structure and thus not much reliance can be placed on its length of 1.56Å. It is certainly not significantly

greater than the value of 1.49Å quoted for nitrobenzene (Trotter, 1959). Zhdanov and Golder (1955) suggested, on the basis of current data, that a lengthening of the carbon-nitrogen bond might be expected when a nitro-group was twisted out of the plane of the benzene ring. This effect they attributed to a reduction of conjugation. Subsequent results have not confirmed this theory, the values for 4-chloro-3-nitrobenzoic acid (Ferguson, 1961) and nitrobenzene, for example, being almost identical.

The strong steric interaction between axial 1, 3-methyl groups is a well-known phenomenon. On the basis of standard ideal valency bond lengths and angles such atoms would be expected to be 2.52Å apart. The fact that the distance C(19) - C(30) is 3.24Å in the orthorhombic and 3.34Å in the monoclinic case shows that strong repulsive forces must be pushing these atoms away from one another. The respective values of the non-bonded distance C(17) - C(30) are 3.13Å and 3.14Å - again significantly greater than 2.52Å.

That the γ-lactone is non-planar is shown by the fact that its mean internal valency angle is 106° - less than the planar value, 108°. This is in accord with the pattern discussed in section 2.(9). The average valency angle in the benzene ring is the expected value of 120°.

Not much significance can be attached to the size of the O-N-O valency angle of which there is only one example. The value, 114°, is considerably lower than the usual angle of 125° as found in m-dinitrobenzene (Trotter, 1961).

The angles around C(16), C(23), C(31) and C(33) are in accord with the pattern found in carboxylic acids. The average O-C-C angle is 112°, whereas the mean of the O-C = O and C-C = O angles is 123°, i.e. in lactone and ester groupings the angle not involving the carbonyl oxygen is approximately tetrahedral, the other two being considerably greater. The effect is due to repulsion by the lone pairs of electrons on the carbonyl oxygen atom. Further examples of this phenomenon are afforded by bromogeigerin acetate (Hamilton, McPhail and Sim, 1962) where the respective average values are 113° and 124° and by angles of 113° and 123° in o-chlorobenzoic acid (Ferguson and Sim, 1961).

As expected, C(20) is displaced significantly from the plane of the other five atoms in the γ-lactone. The deviation is 0.49Å (Table 25). This pattern has been observed in a considerable number of γ-lactone rings of which that in himbacine hydrobromide (Fridrichsons and Mathieson, 1962) is a typical example, the displacement being 0.61Å. In conformation with this pattern, it is

found that only C(8) and C(14) markedly deviate from the plane of the other five atoms of the δ-lactone system. C(14) (0.54Å) is displaced further from the plane than C(8) (0.27Å). This is presumably due to the fact that the latter atom is more firmly held by the molecular framework, being at the junction of three six-membered rings.

None of the atoms of the acetoxy - or the nitro-groups are displaced significantly from their mean planes.

The atoms and direct substituents of the benzene ring can be taken as coplanar, but the oxygens of the ester and nitro-groups deviate significantly from the plane of the other atoms. The nitrogen-iodine distance, 3.47Å, is considerably less than the minimum van der Waals' separation of 3.65Å. This shows that this part of the molecule is under considerable steric strain. The strain imposed by the bulky nitro-group in the ortho-position to the iodine atom is partially relieved by a rotation of the nitro-group with respect to the benzene ring about the exocyclic C(36) - N bond. The angle of tilt of the nitro-group to the benzene ring is 87°. This value is very much greater than 49° and 46° quoted by Ferguson (1961) for these angles in 4-bromo-and 4-chloro-3-nitrobenzoic acids. Presumably the difference could be caused by the greater bulk of the ortho-iodine atom or by the crystal forces present in the

simarolide derivative. The size of this angle in 4-iodo-3-nitrobenzoic acid would be interesting.

The ester group is inclined to the benzene ring plane at an angle of about 11°, which is in agreement with the values of 9° and 7° for the above-mentioned substituted benzoic acids (Ferguson, 1961). This twist of the C(33) - C(34) exocyclic bond, has been attributed to a buttressing effect due to the bulky nitro-group and relayed by the hydrogen atom at C(35) which is displaced from its ideal position in the direction of O(2). This hydrogen - O(2) interaction causes the ester group to rotate out of the plane of the benzene ring. (Ferguson and Sim, 1962a).

As was observed with 4-bromo-3-nitrobenzoic acid (Ferguson, 1961), the oxygen atom of the nitro-group and that of the ester which approach most closely - O(2) and O(11) - are both displaced on the same side of the benzene ring mean plane. A difference exists, however, in that the carbonyl oxygen is the nearer atom to the nitro-group in the simple acid and the more distant atom in the simarolide derivative.

TABLE 20

Simarolide 4-iodo-3-nitrobenzoate

Latest Atomic Coordinates and α-values

Atom	x/a	y/b	z/c	α ($0.607\beta_e$)
C(1)	-0.1984	0.1007	0.2422	2.85
C(2)	-0.2333	0.0509	0.2757	3.09
C(3)	-0.3025	0.0645	0.3546	3.15
C(4)	-0.3010	0.0977	0.5465	2.95
C(5)	-0.2555	0.1450	0.5069	2.74
C(6)	-0.2615	0.1825	0.6391	2.97
C(7)	-0.2220	0.2300	0.6122	2.66
C(8)	-0.1508	0.2184	0.5735	2.93
C(9)	-0.1440	0.1781	0.4019	2.95
C(10)	-0.1888	0.1301	0.4468	2.96
C(11)	-0.0753	0.1710	0.3819	2.75
C(12)	-0.0375	0.2174	0.3198	3.42
C(13)	-0.0507	0.2641	0.4458	3.17
C(14)	-0.1232	0.2697	0.4946	2.94
C(15)	-0.1626	0.2781	0.3098	2.98
C(16)	-0.2295	0.2796	0.3139	2.80
C(17)	-0.0002	0.2670	0.6406	3.07
C(18)	-0.0242	0.3125	0.3266	3.49
C(19)	-0.1555	0.0969	0.6128	3.24
C(20)	0.0646	0.2480	0.6347	3.12
C(21)	0.0703	0.1955	0.6840	3.96
C(22)	0.1066	0.2742	0.8033	3.86
C(23)	0.1039	0.2405	0.9704	4.16
C(28)	-0.3703	0.1097	0.6076	3.06

TABLE 20 (Contd.)

Atom	x/a	y/b	z/c	α
C(30)	-0.1210	0.2070	0.7886	3.03
C(31)	-0.0151	0.1035	0.2341	3.91
C(32)	0.0033	0.0776	0.0226	3.56
C(33)	-0.1866	-0.0014	0.0027	3.91
C(34)	-0.2093	-0.0245	-0.1967	3.01
C(35)	-0.2713	-0.0350	-0.2445	2.98
C(36)	-0.2780	-0.0608	-0.4172	3.18
C(37)	-0.2261	-0.0836	-0.5346	3.34
C(38)	-0.1614	-0.0755	-0.4653	3.03
C(39)	-0.1557	-0.0455	-0.3107	3.16
O(1)	-0.1935	0.1202	0.0731	3.10
O(2)	-0.2430	0.0264	0.0821	3.13
O(3)	-0.1411	0.0034	0.1081	4.00
O(4)	-0.2577	0.2509	0.4437	2.83
O(5)	-0.0638	0.1356	0.2087	3.08
O(6)	0.0173	0.1019	0.3879	3.49
O(7)	-0.2681	0.3063	0.1897	3.50
O(8)	0.0735	0.1942	0.9108	3.98
O(9)	0.1120	0.2487	1.1632	4.13
O(10)	-0.0264	0.2889	0.7885	3.62
O(11)	-0.3920	-0.0379	-0.5668	5.20
O(12)	-0.3734	-0.0989	-0.3690	4.96
N	-0.3500	-0.0673	-0.4822	3.32
I	-0.2403	-0.1275	-0.7987	4.21

Coordinates of the four possible atoms of solvent molecule -

Atom	x/a	y/b	z/c
C(40)	-0.0288	0.4122	0.0859
C(41)	0.0137	0.4402	0.0250
C(42)	0.0598	0.4735	0.0464
C(43)	0.0129	0.5502	-0.0886

TABLE 21

SIMAROLIDE

Comparative Bond Lengths (Å)

	O	M	Mean			O	M	Mean
C(1) ... C(2)	1.53	1.58	1.56	C(16) ... O(4)		1.28	1.41	1.35
C(1) ... C(10)	1.54	1.56	1.55	C(16) ... O(7)		1.34	1.26	1.30
C(1) ... O(1)	1.23	1.21	1.22	C(17) ... O(10)		1.25	1.31	1.28
C(2) ... C(3)	1.57	1.58	1.58	C(17) ... C(20)		1.44	1.56	1.50
C(2) ... O(2)	1.44	1.38	1.41	C(20) ... C(21)		1.45	1.45	1.45
C(3) ... C(4)	1.54	1.80	1.67	C(20) ... C(22)		1.57	1.55	1.56
C(4) ... O(5)	1.60	1.50	1.55	C(21) ... O(8)		1.48	1.45	1.47
C(4) ... C(28)	1.52	1.47	1.50	C(22) ... C(23)		1.42	1.50	1.46
C(5) ... C(10)	1.51	1.55	1.53	C(23) ... O(8)		1.44	1.22	1.33
C(5) ... C(6)	1.33	1.48	1.41	C(23) ... O(9)		1.29	1.21	1.25
C(6) ... C(7)	1.52	1.59	1.56	C(31) ... O(5)		1.34	1.33	1.34
C(7) ... C(8)	1.53	1.59	1.56	C(31) ... O(6)		1.21	1.25	1.23
C(7) ... O(4)	1.44	1.63	1.54	C(31) ... C(32)		1.59	1.38	1.49
C(8) ... C(9)	1.56	1.52	1.54	C(33) ... O(2)		1.48	1.48	1.48
C(8) ... C(14)	1.57	1.54	1.56	C(33) ... O(3)		1.02	1.22	1.12
C(8) ... C(30)	1.56	1.57	1.57	C(33) ... C(34)		1.52	1.43	1.48
C(9) ... C(10)	1.57	1.56	1.57	C(34) ... C(35)		1.35	1.42	1.39
C(9) ... C(11)	1.44	1.48	1.46	C(35) ... C(36)		1.33	1.35	1.34
C(10) ... C(19)	1.58	1.53	1.56	C(36) ... C(37)		1.46	1.34	1.40
C(11) ... C(12)	1.52	1.65	1.59	C(37) ... C(38)		1.33	1.43	1.38
C(11) ... O(5)	1.49	1.49	1.49	C(38) ... C(39)		1.28	1.36	1.32
C(12) ... C(13)	1.52	1.65	1.59	C(39) ... C(34)		1.45	1.36	1.41
C(13) ... C(14)	1.54	1.52	1.53	C(36) ... I		-	1.95	
C(13) ... C(17)	1.65	1.58	1.62	C(37) ... I		2.11	-	
C(13) ... C(18)	1.61	1.55	1.58	C(36) ... N		1.56	-	
C(14) ... C(15)	1.47	1.53	1.50	N ... O(11)		1.30	-	
C(15) ... C(16)	1.39	1.43	1.41	N ... O(12)		1.22	-	

TABLE 22

SIMAROLIDE

Comparative Bond Angles

	O	M	Mean
O(1)C(1)C(2)	123°	125°	124°
O(1)C(1)C(10)	123	137	130
C(10)C(1)C(2)	112	99	106
C(1)C(2)O(2)	110	103	107
C(1)C(2)C(3)	106	108	107
O(2)C(2)C(3)	106	96	101
C(2)C(3)C(4)	113	121	117
C(3)C(4)C(5)	110	96	103
C(3)C(4)C(28)	108	104	106
C(28)C(4)C(5)	116	121	119
C(4)C(5)C(10)	112	121	117
C(4)C(5)C(6)	116	104	110
C(6)C(5)C(10)	117	111	114
C(5)C(6)C(7)	120	125	123
C(6)C(7)C(8)	112	106	109
C(6)C(7)O(4)	98	93	96
O(4)C(7)C(8)	117	99	108
C(7)C(8)C(9)	110	120	115
C(7)C(8)C(14)	103	106	105
C(7)C(8)C(30)	106	96	101
C(30)C(8)C(9)	118	120	119
C(30)C(8)C(14)	109	99	104
C(9)C(8)C(14)	110	113	112
C(8)C(9)C(10)	112	112	112
C(8)C(9)C(11)	104	109	107
C(10)C(9)C(11)	119	115	117
C(9)C(10)C(5)	112	116	114
C(1)C(10)C(5)	104	97	101
C(9)C(10)C(1)	109	108	109
C(19)C(10)C(1)	111	116	114
C(19)C(10)C(9)	109	109	109
C(19)C(10)C(5)	112	110	111
C(9)C(11)C(12)	115	112	114
C(9)C(11)O(5)	108	111	110
C(12)C(11)O(5)	103	98	101
C(11)C(12)C(13)	116	112	114
C(12)C(13)C(14)	112	112	112
C(12)C(13)C(18)	110	108	109
C(12)C(13)C(17)	110	109	110
C(18)C(13)C(17)	97	95	96
C(17)C(13)C(14)	117	109	113
C(18)C(13)C(14)	111	122	117
C(13)C(14)C(8)	110	120	115
C(13)C(14)C(15)	113	104	109
C(8)C(14)C(15)	102°	105°	104°
C(14)C(15)C(16)	123	126	125
C(15)C(16)O(4)	117	114	116
C(15)C(16)O(7)	127	133	130
O(7)C(16)O(4)	116	113	115
C(13)C(17)C(20)	124	124	124
C(13)C(17)O(10)	110	109	110
O(10)C(17)C(20)	126	117	122
C(17)C(20)C(21)	114	116	115
C(17)C(20)C(22)	110	114	112
C(21)C(20)C(22)	103	95	99
C(20)C(21)O(8)	104	112	108
C(20)C(22)C(23)	104	104	104
C(22)C(23)O(8)	111	111	111
C(22)C(23)O(9)	130	130	130
O(8)C(23)O(9)	118	111	115
O(5)C(31)O(6)	123	124	124
O(5)C(31)C(32)	111	116	114
O(6)C(31)C(32)	125	119	122
O(2)C(33)O(3)	116	109	113
O(2)C(33)C(34)	105	108	107
O(3)C(33)C(34)	138	131	135
C(33)C(34)C(35)	125	128	127
C(33)C(34)C(39)	111	115	113
C(39)C(34)C(35)	122	117	120
C(34)C(35)C(36)	114	128	121
C(35)C(36)C(37)	126	126	126
C(35)C(36)N	113	-	
N C(36)C(37)	121	-	
C(36)C(37)C(38)	114	116	115
C(37)C(38)C(39)	124	107	116
C(38)C(39)C(34)	119	123	121
C(36)C(37)I	124	-	
I C(37)C(38)	122	-	
C(2)O(2)C(33)	115	122	119
C(7)O(4)C(16)	120	123	122
C(11)O(5)C(31)	116	119	118
C(21)O(8)C(23)	106	109	108
C(36) N O(11)	134	-	
C(36) N O(12)	107	-	
O(11) N O(12)	114	-	
C(35)C(36) I	-	120	
I C(36)C(37)	-	114	

TABLE 23

SIMAROLIDE

Some comparative intramolecular non-bonded Distances (Å) (<4Å)

	O	M	Mean
C(1) ...O(2)	2.43	2.39	2.41
C(1) ... C(33)	3.15	3.17	3.16
C(1) ... O(3)	3.02	3.17	3.10
C(2) ... O(3)	2.57	2.51	2.54
C(3) ... C(28)	2.48	2.59	2.54
C(5) ... C(28)	2.64	2.58	2.61
C(6) ... C(28)	2.99	2.96	2.98
C(6) ... O(4)	2.23	2.33	2.28
C(6) ... C(30)	3.14	3.12	3.13
C(6) ... C(19)	3.18	3.32	3.25
C(7) ... C(30)	2.47	2.38	2.43
C(8) ... C(19)	3.26	3.33	3.30
C(9) ... O(5)	2.38	2.44	2.41
C(9) ... C(19)	2.58	2.66	2.62
C(9) ... C(30)	2.68	2.76	2.72
C(10) ... C(30)	3.45	3.40	3.43
C(11) ... C(19)	2.99	2.96	2.98
C(11) ... C(30)	2.98	3.13	3.06
C(12) ... C(30)	3.53	3.77	3.65
C(13) ... C(30)	3.07	3.21	3.14
C(13) ... O(10)	2.39	2.49	2.44
C(13) ... C(21)	3.47	3.53	3.50
C(14) ... C(30)	2.55	2.44	2.50
C(15) ... O(7)	2.44	2.47	2.46
C(15) ... C(30)	3.76	3.79	3.78
C(17) ... C(18)	2.44	2.31	2.38
C(17) ... C(30)	3.13	3.14	3.14
C(19) ... C(30)	3.24	3.34	3.29
C(19) ... O(1)	3.66	3.55	3.61
C(22) ... O(9)	2.45	2.47	2.46
C(22) ... O(10)	2.79	2.85	2.82
C(32) ... O(6)	2.49	2.43	2.46
O(1) ... O(2)	2.71	2.65	2.68
O(2) ... O(3)	2.10	2.23	2.17
O(4) ... O(7)	2.23	2.23	2.23
O(5) ... O(6)	2.24	2.35	2.30
O(8) ... O(9)	2.34	2.00	2.17
O(11) .. O(12)	2.12	-	
I ... N	3.47	-	

TABLE 24

Simarolide 4-iodo-3-nitrobenzoate

Intermolecular Non-bonded distances (Å) (<4Å)

C(39) ... $C(15)_I$	3.93	C(21) ... $O(4)_V$	3.93
C(32) ... $O(3)_I$	3.68	C(18) ... $C(28)_V$	3.83
O(9) ... $O(7)_{II}$	3.69	C(20) ... $O(7)_V$	3.93
C(16) ... $O(12)_{III}$	3.90	C(20) ... $O(4)_V$	3.72
C(15) ... $O(12)_{III}$	3.39	C(23) ... $C(16)_V$	3.96
C(18) ... $O(12)_{III}$	3.19	C(23) ... $O(7)_V$	3.11
C(14) ... $O(12)_{III}$	3.61	C(23) ... $O(4)_V$	3.95
O(7) ... $C(36)_{III}$	3.97	C(22) ... $C(16)_V$	3.77
O(7) ... $C(37)_{III}$	3.71	C(22) ... $O(7)_V$	3.37
O(7) ... $C(38)_{III}$	3.93	C(22) ... $O(4)_V$	3.31
O(4) ... I_{III}	3.99	O(8) ... $O(7)_V$	3.35
C(21) ... $C(38)_{IV}$	3.96	O(9) ... $C(6)_V$	3.45
O(6) ... $C(39)_{IV}$	3.79	O(9) ... $C(7)_V$	3.78
O(6) ... $C(38)_{IV}$	3.34	O(9) ... $O(4)_V$	3.73
C(21) ... $O(7)_V$	3.45	O(7) ... I_{VI}	3.11

The subscripts refer to the following equivalent positions -

I	$-x$	$-y$	z	IV	$-x$, $-y$, $z + 1$
II	$\frac{1}{2} + x$,	$\frac{1}{2} - y$,	$-z$	V	$\frac{1}{2} + x$, $\frac{1}{2} - y$, $1 - z$
III	$-\frac{1}{2} + x$,	$\frac{1}{2} - y$,	$-z$	VI	$-\frac{1}{2} + x$, $\frac{1}{2} - y$, $-1 - z$

TABLE 25

Simarolide 4-iodo-3-nitrobenzoate

Deviations (Å) of atoms from mean planes

a) γ-lactone - plane defined by C(21),C(22),C(23),O(8),O(9)

Atom	Deviation	Atom	Deviation
C(21)	+0.04	O(8)	-0.07
C(22)	-0.04	O(9)	Nil
C(23)	+0.07	C(20)	-0.49

b) δ-lactone - plane defined by C(7),C(15),C(16),O(4),O(7)

Atom	Deviation	Atom	Deviation
C(7)	+0.09	O(7)	+0.06
C(15)	-0.02	C(8)	-0.27
C(16)	-0.01	C(14)	+0.54
O(4)	-0.13		

c) Acetoxy group - plane defined by C(11),C(31),C(32),O(5),O(6)

Atom	Deviation	Atom	Deviation
C(11)	+0.09	O(5)	-0.09
C(31)	-0.09	O(6)	+0.09
C(32)	+0.08		

d) Benzene ring and substituents - plane defined by C(33),C(34),C(35),C(36),C(37),C(38),C(39),N,I.

Atom	Deviation	Atom	Deviation
C(33)	-0.11	N	+0.04
C(34)	+0.08	I	-0.06
C(35)	-0.03	O(2)	+0.17
C(36)	+0.01	O(3)	-0.23
C(37)	-0.02	O(11)	+0.96
C(38)	+0.01	O(12)	-1.09
C(39)	+0.08		

TABLE 25 (Contd.)

e) Carbon -nitro-group - plane defined by C(36), N, O(11), O(12)

Atom	Deviation	Atom	Deviation
C(36)	-0.04	O(11)	-0.05
N	+0.13	O(12)	-0.04

Interplanar angle between (d) and (e) = 87°.

TABLE 26

Simarolide m-iodobenzoate

Latest atomic coordinates and α-values
(Origin of coordinates on two-fold screw axis)

Atom	x/a	y/b	z/c	α ($0.607B_e$).
C(1)	0.3118	-0.3348	-0.1866	2.78
C(2)	0.2737	-0.4260	-0.1152	2.98
C(3)	0.3565	-0.4911	-0.0750	4.03
C(4)	0.4119	-0.7069	-0.1126	3.00
C(5)	0.4199	-0.6086	-0.1791	2.70
C(6)	0.4765	-0.7582	-0.2151	2.91
C(7)	0.4984	-0.7395	-0.2912	2.67
C(8)	0.4011	-0.6544	-0.3291	2.86
C(9)	0.3413	-0.4928	-0.2971	2.73
C(10)	0.3276	-0.5408	-0.2224	2.90
C(11)	0.2497	-0.4615	-0.3390	2.75
C(12)	0.2692	-0.3722	-0.4133	3.24
C(13)	0.3502	-0.5103	-0.4492	3.12
C(14)	0.4277	-0.5936	-0.3990	2.90
C(15)	0.4995	-0.4170	-0.3882	2.83
C(16)	0.5582	-0.3716	-0.3282	2.78
C(17)	0.2968	-0.6944	-0.4868	2.88
C(18)	0.3763	-0.3990	-0.5130	3.35
C(19)	0.2473	-0.6998	-0.2186	3.09
C(20)	0.1914	-0.6819	-0.5206	3.12
C(21)	0.1169	-0.7884	-0.4871	3.96
C(22)	0.1814	-0.8143	-0.5843	3.86
C(23)	0.1480	-1.0167	-0.5600	4.16
C(28)	0.4992	-0.7468	-0.0678	3.03
C(30)	0.3549	-0.8676	-0.3459	3.03

TABLE 26 (Contd.)

Atom	x/a	y/b	z/c	α
C(31)	0.1017	-0.2611	-0.3343	3.81
C(32)	0.0532	-0.1092	-0.3029	3.49
C(33)	0.1764	-0.1085	-0.0900	4.00
C(34)	0.1683	0.0529	-0.0428	3.07
C(35)	0.2282	0.0894	0.0169	2.94
C(36)	0.2205	0.2404	0.0611	3.65
C(37)	0.1629	0.4060	0.0522	3.18
C(38)	0.0698	0.3878	-0.0133	2.98
C(39)	0.0853	0.1640	-0.0520	2.96
O(1)	0.3159	-0.1565	-0.2005	3.12
O(2)	0.2587	-0.2522	-0.0793	3.07
O(3)	0.1164	-0.1747	-0.1318	3.94
O(4)	0.5563	-0.5252	-0.2792	2.83
O(5)	0.1957	-0.2825	-0.3153	3.01
O(6)	0.0528	-0.3871	-0.3694	3.52
O(7)	0.6065	-0.2181	-0.3083	3.56
O(8)	0.1042	-0.9954	-0.5104	3.98
O(9)	0.1205	-1.1674	-0.5908	4.13
O(10)	0.3448	-0.8632	-0.4942	3.57
I	0.3089	0.2512	0.1414	4.79

Coordinates of the four possible atoms of solvent molecule -

Atom	x/a	y/b	z/c
C(40)	0.7892	0.2469	0.7524
C(41)	0.8574	0.2212	0.8008
C(42)	0.8667	0.2599	0.8250
C(43)	0.9348	0.0476	0.7865

TABLE 27

Simarolide m-iodobenzoate

Intermolecular non-bonded distances (Å) (<4Å)

C(38) ... $C(39)_I$	3.26	C(3) ... $C(28)_{II}$	3.73
C(38) ... $C(34)_I$	3.94	I ... $O(7)_{II}$	3.48
C(38) ... $O(3)_I$	3.92	I ... $O(4)_{II}$	3.70
C(37) ... $C(39)_I$	3.82		

The subscripts refer to the following equivalent positions -

I $-x, \frac{1}{2} + y, -z$ II $-x + 1, \frac{1}{2} + y, -z$

TABLE 28

Simarolide m-iodobenzoate

Course of Stucture analysis.

Operation	Atoms included	R(%)
2D hol Patterson synthesis	-	-
1st 3D Fourier synthesis	I	44.1
2nd 3D " "	I+10(C)	40.9
3rd 3D " "	I+12(C)	40.0
4th 3D " "	I+20(C)	36.8
5th 3D " "	I+9(C)	41.2
6th 3D " "	I+17(C)+16(C)$_{\frac{1}{2}}$	35.4
7th 3D " "	I+18(C)+24(C)$_{\frac{1}{2}}$	33.5
8th 3D " "	I+34(C)+2(C)$_{\frac{1}{2}}$+3(O)	28.9
Two rounds (F_o-F_c) synthesis	"	26.9
9th 3D Fourier synthesis	I+36(C)+10(O)	25.9
10th 3D " "	I+38(C)+10(O)	24.7
F_o and F_c synthesis	"	24.1
11th 3D Fourier synthesis	I+34(C)+10(O)	24.6

TABLE 29

Simarolide 4-iodo-3-nitrobenzoate

Course of structure analysis

Operation	Atoms included	R(%)
Two 2D Patterson syntheses	-	-
1st 3D Fourier synthesis	I	38.8
2nd 3D " "	I+31(C)+N+8(O)	26.2
3rd 3D " "	I+34(C)+10(O)	22.3
4th 3D " "	I+37(C)+N+12(O)	22.4
(F_o-F_c) synthesis	"	22.1
F_o and F_c synthesis	"	22.1
5th 3D Fourier synthesis	I+34(C)+N+12(O)	21.6

Table 30 Simarolide 4-iodo-3-nitrobenzoate

Latest observed and calculated values of the structure factors.

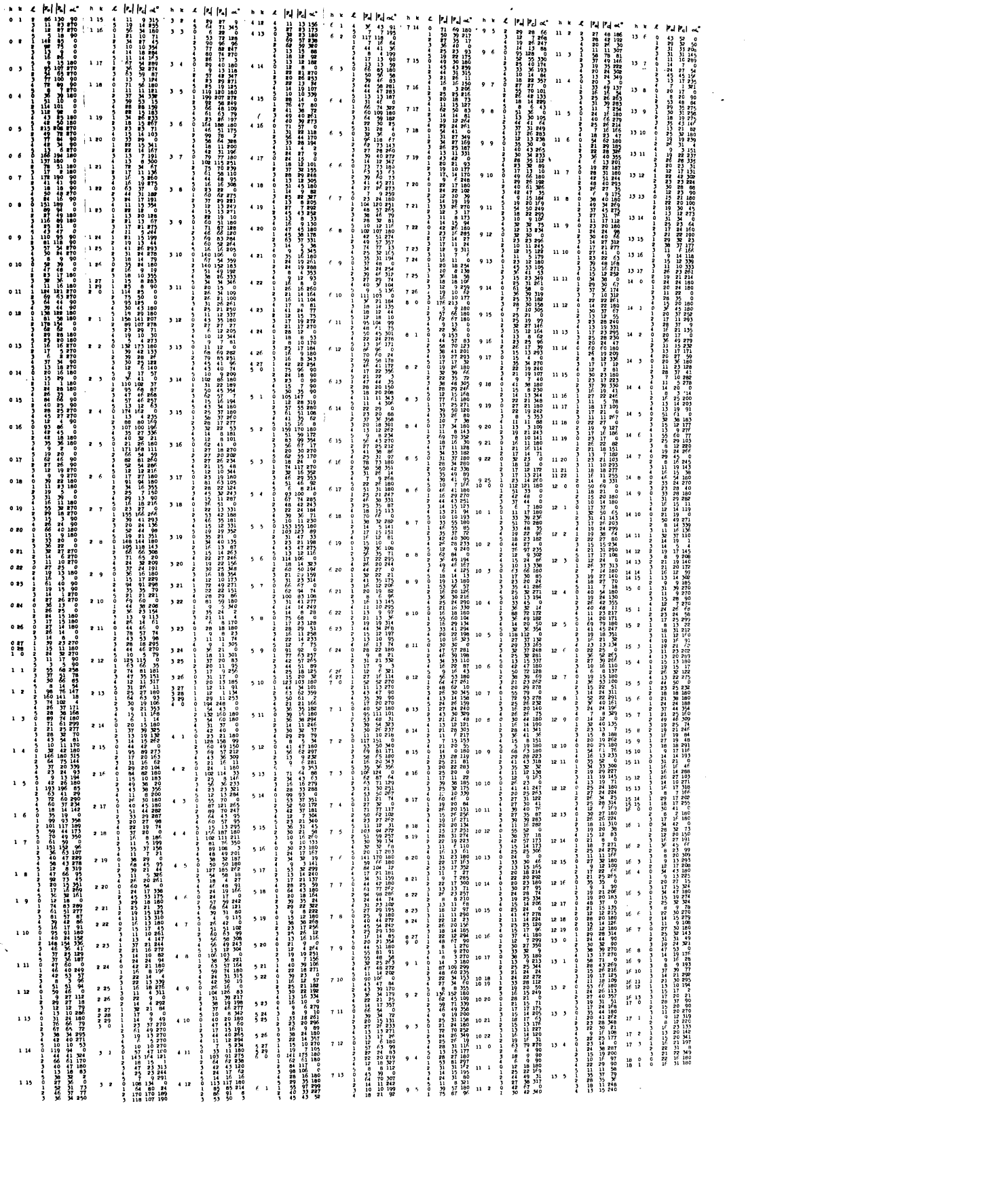
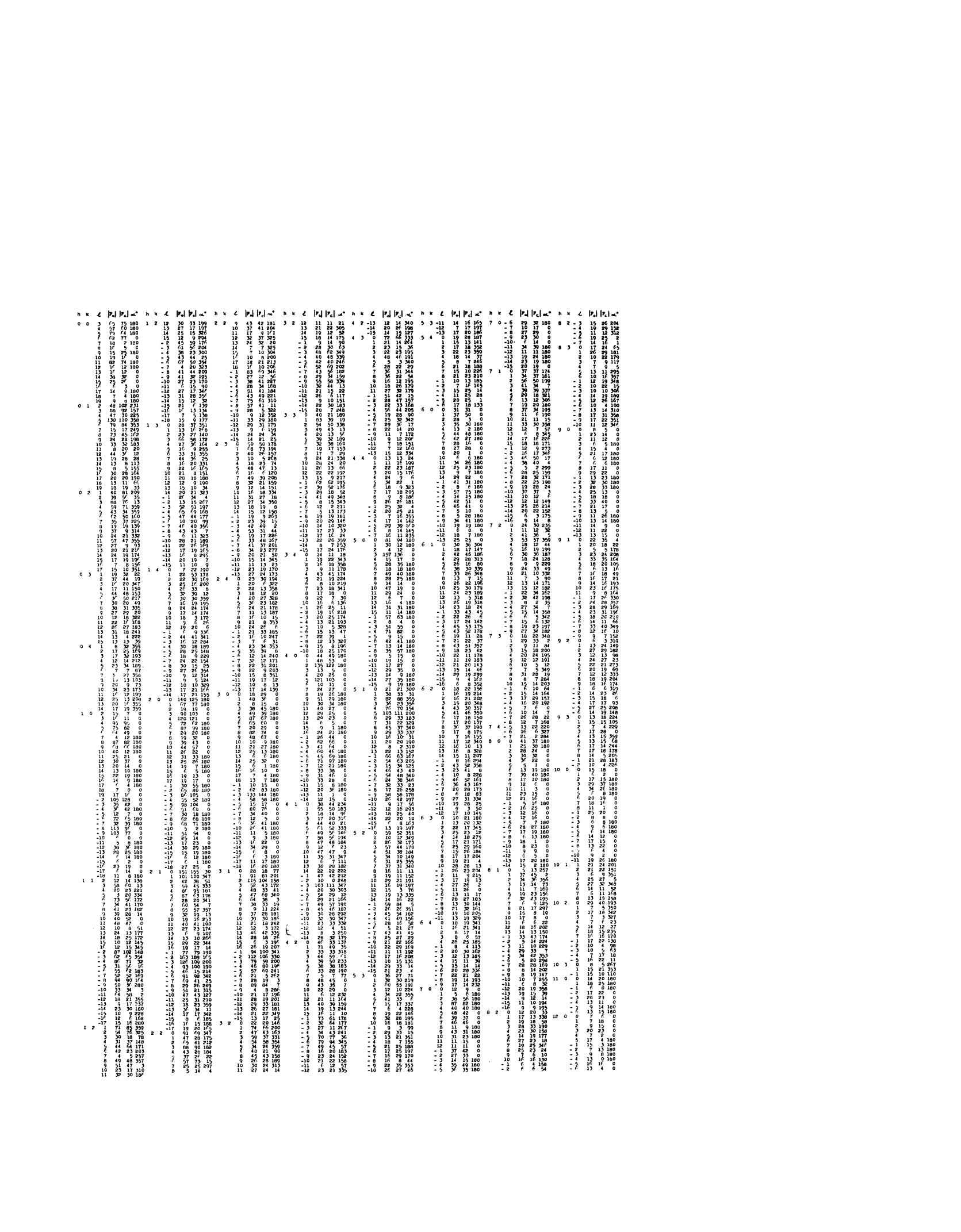


Table 31 Simarolide m-iodobenzoate

Latest observed and calculated values of the structure factors.



PART V

THE STRUCTURE OF A COMPOUND FORMED BY THE REACTION OF DIPHENYLKETEN AND ETHOXYACETYLENE: X-RAY ANALYSIS OF THE CHROMIUM TRICARBONYL ADDUCT

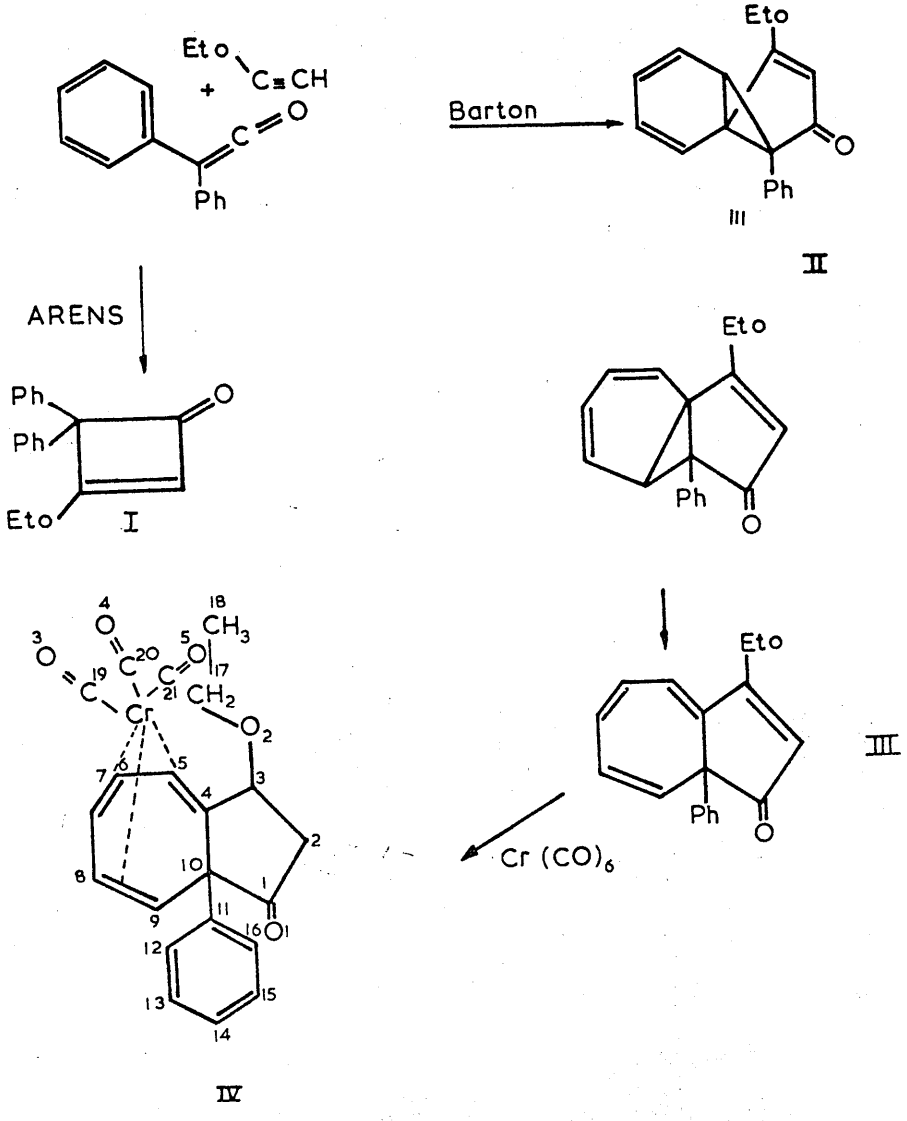

Eto
C≡CH
+
C
O
Ph
Barton
Eto
O
Ph
III
II
ARENS
Ph
Ph
O
Eto
I
Eto
Ph
O
4
O
18
CH3
3
O
5
O
17
C20
C19
C21
CH2
Cr
O2
7
6
5
4
3
2
8
10
1
9
11
16
O1
12
13
15
14
IV
Eto
Ph
O
III
Cr (CO)6

Fig. 33

5.(1). Introduction.

Nieuwenhuis and Arens (1958) proposed that the product which they had obtained by the reaction of diphenylketen and ethoxyacetylene in nitromethane at reduced temperature was 3-ethoxy-4,4-diphenyl-cyclobutenone (I) (Fig. 33). This postulate was later withdrawn with no substitute explanation given.

The problem was taken up by Barton and his co-workers (1962) who repeated the reaction and then prepared a chromium tricarbonyl complex of the product and handed these crystals over for x-ray analysis.

The x-ray analysis has proved to be very slow and stubborn- so much so that the chemical analysis was finished and published early in 1962, whereas the structure obtained by diffraction methods is still at an early stage of refinement.

Barton (1962) was able to show by conventional chemical and spectroscopic methods that the reaction involved the rather curious rearrangements shown in II and III in Fig. 33. III was the final product Nieuwenhuis and Arens had obtained, and the chromium carbonyl compound which was supplied to us is shown at IV.

5.(2). Experimental.

The usual x-ray photographs were taken using copper - K_α (λ = 1.5418Å) and molybdenum - K_α (λ = 0.7107Å) radiations. The unit cell parameters were measured from precession and rotation photographs as previously. The data was collected as before, no absorption corrections being made. Due to serious fluorescent scattering of copper radiation by chromium atoms, all the data was collected using molybdenum - K_α radiation and the precession camera. The intensities of zones Okl, -----, 4kl and hko, -----, hk5 were estimated visually. The individual series were collected by sets of timed exposures. In all, 4,476 intensity estimations were made of which 2,970 were from independent planes and 736 were below the minimum observable value.

The intensity values were reduced to structure amplitudes using the charts due to Grenville-Wells and Abrahams (1952).

The values of $|F_o|$ were put on an approximately absolute scale by correlation with $|F_c|$ values at various stages in the analysis.

Potassium iodide solutions were used in the measurement of crystal density.

5.(3). Crystal Data.

$C_{21}H_{16}O_5Cr$ — M = 400.4

Triclinic — a = 11.71 ± 0.04Å

b = 12.78 ± 0.03Å

c = 13.47 ± 0.06Å

$\alpha = 87^{\circ}0'$

Volume of unit cell = 1,820Å^3 — $\beta = 109^{\circ}45'$

$\gamma = 106^{\circ}26'$

For z = 4, D(Calculated) = 1.46 g./cc.

D(Observed) = 1.44 g./cc.

F(000) = 824

Linear absorption coefficient for x-rays (λ = 0.7107Å)

μ = 6.9 cm.$^{-1}$.

Since the crystal is triclinic there are no systematically absent reflections, and as in the case of BROS (Section 3.(3).), the space group assigned was $P\bar{1}$.

The fact that there are only two equivalent positions in $P\bar{1}$ whereas there are four molecules per unit cell shows that there must be two molecules in the asymmetric unit i.e. two molecules which are chemically identical but crystallographically distinct. This feature generally facilitates analysis, as different structural features of the skeleton may appear on the Fourier map in the two non-symmetrically related molecules and this knowledge enables atoms to be counted

which are barely resolved. A good example of this procedure is shown in the analysis of epilimonol iodoacetate (Arnott et al., 1961).

5.(4). Location of the Heavy Atom Positions.

As there are two heavy atoms present in the asymmetric unit and the space group is $P\bar{1}$, the analyses of the two-dimensional and three-dimensional Patterson functions are identical with the case of BROS discussed in section 3.(4). This being so, no further relevant comment need be made than that it was possible to locate the heavy atom positions from all three axial projections and that better coordinates were then obtained from the three-dimensional Patterson map. These coordinates were -

Cr. I	x/a = 0.8039	y/b = 0.2227	z/c = 0.0884
Cr.II	x/a = 0.7592	y/b = 0.7331	z/c = 0.4282

5.(5). Solution of the Structure.

Application of the test devised by Sim (1957) and discussed in section 3.(5). showed that approximately 70% of the structure factors would be correctly sign-determined by the contributions of the chromium atoms alone. Normally it would be preferable to have a higher percentage than this, but it was decided to proceed with the analysis.

The above coordinates and an assumed isotropic temperature factor of α = 3.0 were used in the first structure factor calculation and the overall value of the discrepancy, R, was 55.0%.

In cases where there were reflections common to two zones, the structure factors from the hko, ----, hk5 reciprocal lattice nets were employed as Fourier coefficients, till such a time as the mean $|F_o|$ values could be confidently assigned.

Of the independent structure factor values, 944 were deemed not to have been definitely sign-determined, and were omitted from the first Fourier summation.

From the resulting map it was possible to pick out 44 of the 54 atoms in the asymmetric unit. It must be recorded that the structure had, by this time, been elucidated chemically, but this knowledge though helpful was not used if an atom failed to appear in an expected site. The atoms which were not located were C(18), C(19), C(21) O(3) and O(5) in molecule I and C(18), C(13), C(14), C(20) and O(4) in molecule II. In future discussion atoms in molecule II will be referred to with a prime - thus, C(18)'. The coordinates of the 44 atoms were calculated by Booth's method (1948).

These coordinate data and a uniform isotropic temperature factor of α = 3.0 were included in the second structure factor calculation when the discrepancy dropped by 11.2% to 43.8%. This time it was only necessary to reject 594 terms before proceeding to a second Fourier calculation.

All the remaining atoms with the exception of C(18) and C(18)' were clearly resolved in this map, and all the atomic coordinates of the known atoms were evaluated as before. It was found necessary to adjust the coordinates of C(19), C(13)' and C(14)' in order to obtain more realistic bond lengths. The chromium peaks in this map were the only ones which approached their true height, and thus the uniform isotropic temperature factor, α, was raised from 3.0 to 3.5 in all cases except for the heavy atoms.

The discrepancy, summed over all terms, for the following round of structure factors was 37.6% - a drop of 6.2%. 588 of these reflections had values of $|F_o|$ greater than twice $|F_c|$ and were omitted from the next Fourier synthesis.

The positions of C(18) and C(18)' were settled from this map, and the structure confirmed Barton's results.

The new coordinates and same α-values were employed in another phasing calculation for which the overall R-factor was 35.4% - a drop of 2.2%.

5.(6). Refinement of the Structural Parameters.

It was determined to employ difference maps for the initial stages of refinement. Before proceeding, the values of $|F_o|$ for reflections common to two zones were, perhaps rather prematurely, averaged out. It was also decided to omit all the unobserved terms from subsequent calculations.

When this process was completed a further cycle of structure factors was computed and R fell to 32.6%. 269 of these terms had to be excluded before the calculation of a difference map.

A fair number of positional shifts and temperature factor adjustments were indicated by this map. These were applied and the discrepancy over the resultant new structure factors was 30.0%. A further cycle of difference synthesis again showed considerable alterations to the structural parameters. This time the R-factor of the subsequent structure factors, disappointingly, only dropped by 0.5% to 29.5%.

At this stage, further work on this project was postponed. The difficulty of refinement and the high discrepancy are hard to explain. The difference map showed marked signs of anisotropy and perhaps the employment of an isotropic structure factor DEUCE programme retarded refinement. The possibility also exists that the intensity

data are not sufficiently accurate and that there are serious extinction effects causing discrepancies especially in the case of stronger reflections. The Grenville-Wells - Abrahams charts are particularly insensitive to changes in values of Sin Θ at low values of sinΘ where most of the more intense reflections are situated and this may be an additional source of inaccuracy.

It was decided not to recommence this project till new intensity data could be collected from the automatic diffractometer, which, at the time of writing, was still not available for general use.

The course of the structure analysis and refinement is listed in Table 32.

5.(7). Results.

A list of the latest atomic coordinates and α-values is shown in Table 33. From the coordinate data were calculated valency bond lengths, valency bond angles and intramolecular non-bonded distances.

Table 34 gives a list of comparable bond lengths in the non-symmetrically related molecules. The mean value for each bond is also tabulated. A reasonable idea of the accuracy of these parameters may be obtained by finding the root-mean-square deviation of the bond lengths in the two

molecules. This value is about 0.065Å which, on division by $\sqrt{2}$, gives, for the averaged dimensions, a standard deviation of 0.04 - 0.05Å.

Intramolecular non-bonded distances involving the two chromium atoms are given in Table 35.

The closest approach of the two molecules in the asymmetric unit is 3.20Å - the distance between O(5) and O(3)'.

In Table 36 is shown a comparable list to Table 34 involving bond angles instead of bond lengths. The root-mean-square deviation of the bond angles is 6°, giving an e.s.d. for an averaged angle of about 4°.

Various mean plane calculations were performed in the usual manner and deviations from these planes are given in Table 37.

The latest values of $|F_o|$ and $\pm |F_o|$ are listed in Table 38. These are only for reflections whose intensities were equal to or greater than the minimum observable value.

These structure factors were employed in the evaluation of the final F_o map which is portrayed in Fig. 34 as a superimposed electron density contour section map drawn parallel to (001). Fig. 35 shows the corresponding molecular arrangement.

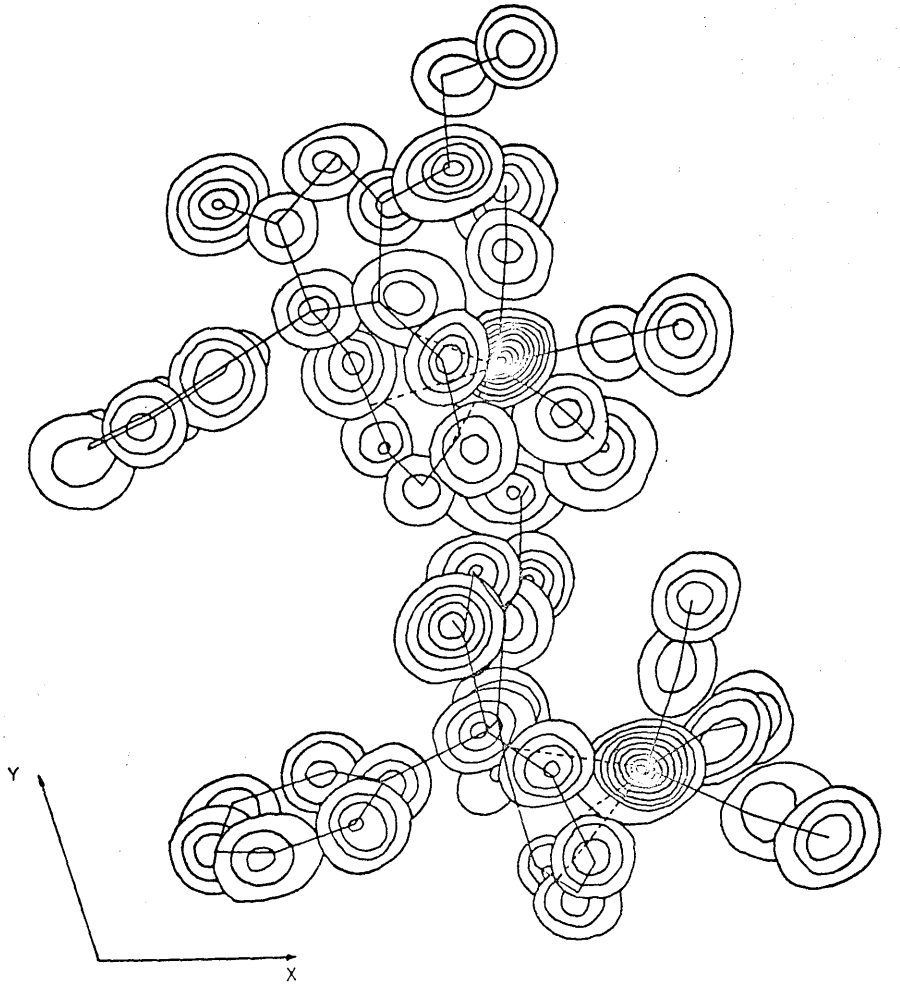


Fig. 34 Chromium carbonyl compound.

Superimposed contour section electron density map drawn parallel to (001). The lowest contour is 2e/Å^3 and all contour intervals are at 1e/Å^3 except for the chromium atoms which are at 2.5e/Å^3.

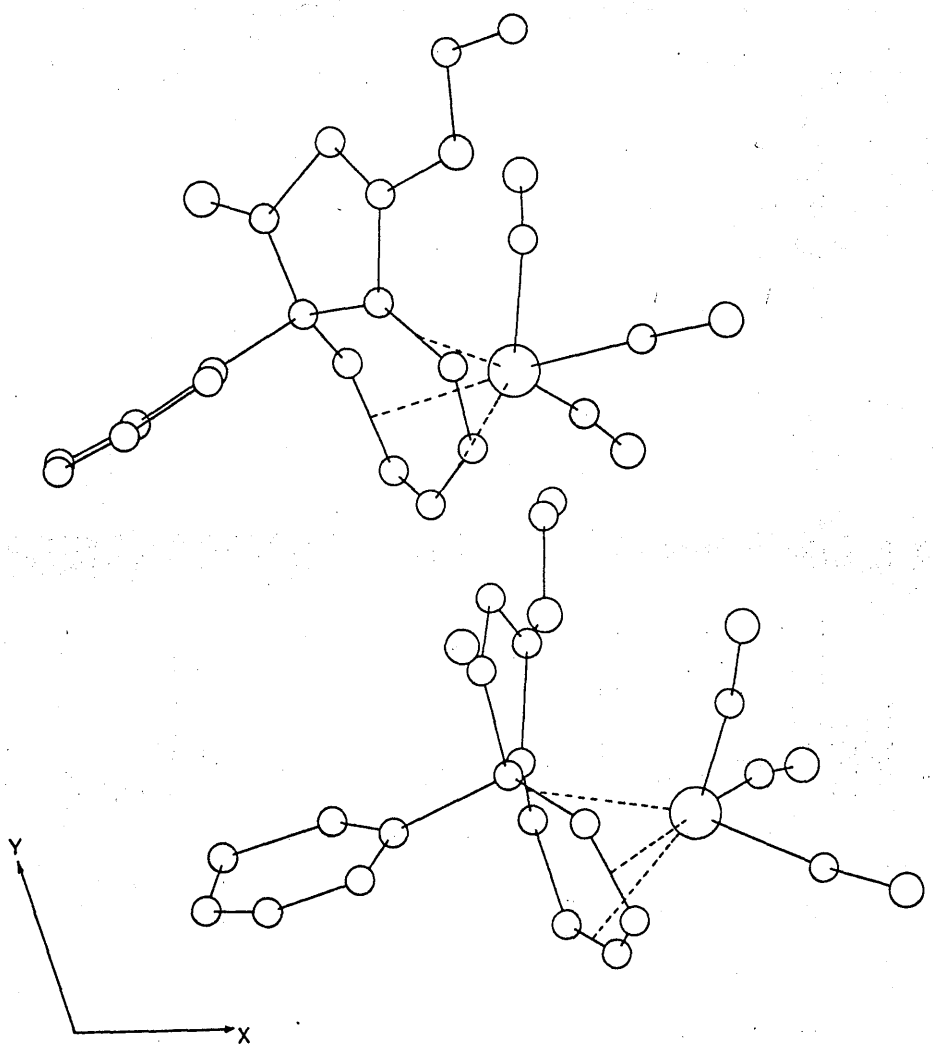


Fig. 35 Chromium carbonyl compound.

Atomic arrangement corresponding to Fig. 34.

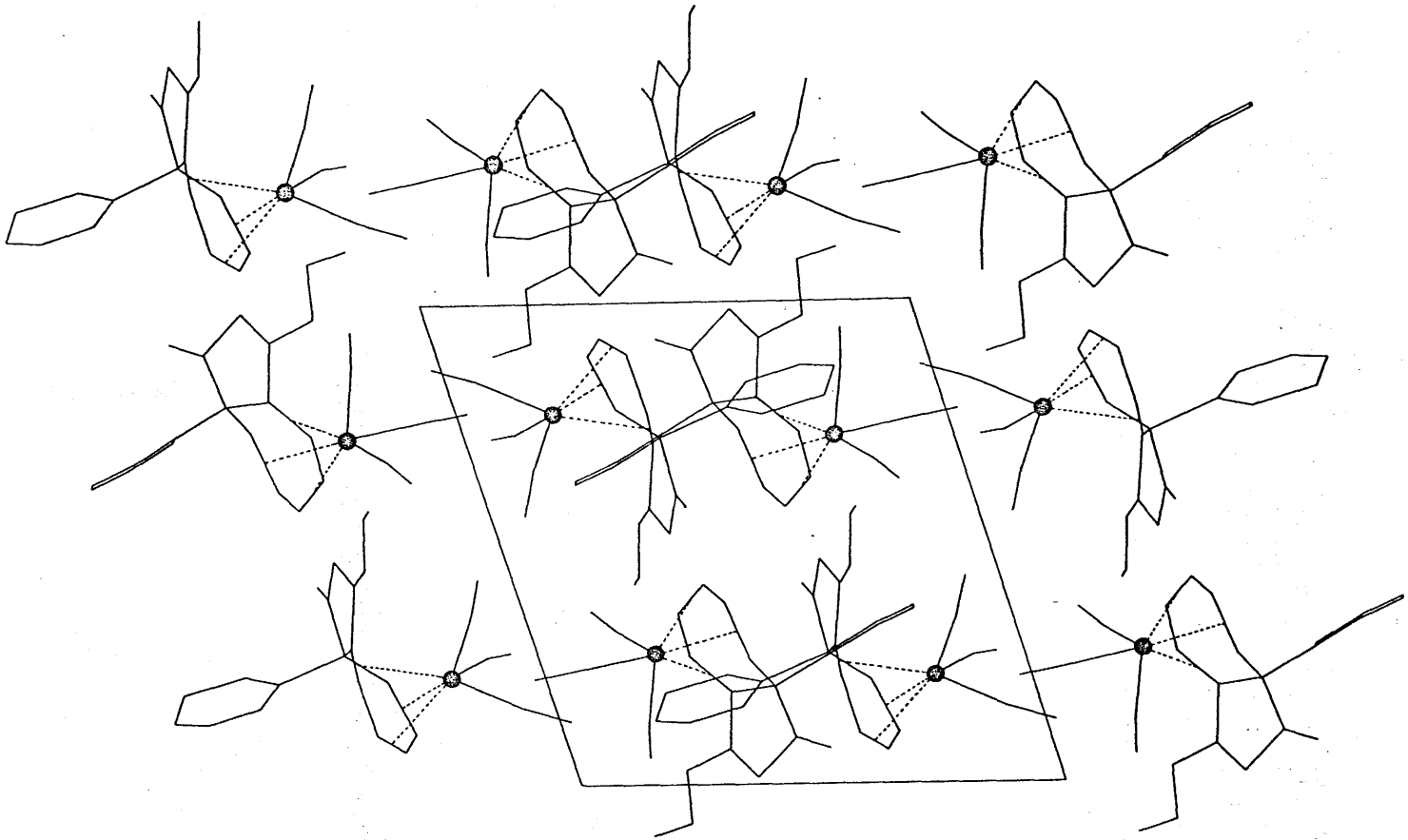


Fig. 36 Chromium carbonyl compound.

Packing diagram as viewed down the c-axis.

The best view of the molecular packing was the projection down the c-axis and this is reproduced in Fig. 36.

5.(8). Discussion.

Since the standard deviations of bond lengths and angles are so large, this discussion, of necessity, is fairly limited since not much stress can be put on small fluctuations of atomic parameters.

The average values of the lengths of the sp^3-carbon-oxygen bond, the sp^2-carbon-oxygen single bond, the sp^2-carbon-oxygen double bond and the carbon-carbon benzene ring bond are 1.42Å, 1.41Å, 1.21Å and 1.36Å. These do not differ significantly from the respective values of 1.46Å, 1.37Å, 1.23Å and 1.40Å given for 5-bromogriseofulvin (section 2.(9).).

Abel et al. (1958) in their discussion of cycloheptatriene metal tricarbonyls, suggested that since the six olefinic carbon atoms in the seven membered ring are almost planar, the six π-electrons might be able to form a delocalised system by by-passing the lone methylene group to form a quasi-aromatic system. This being the case it might be expected that the bond lengths around the ring would not show a pronounced double-bond length - single-bond length

alternation, although it would be unlikely that all the bonds would be of identical length as is the case with benzene.

The average length of the formal single bonds in the conjugated part of the seven-membered ring is 1.45Å whereas that for the double bonds is 1.40Å. These results are possibly not significantly different from the standard values of 1.47Å and 1.34Å respectively, and do not illustrate the above theory convincingly. The phenomenon has been allegedly observed in the structure analysis of tricarbonylcycloocta-1,3,5-trienyl chromium where these average distances are 1.41Å and 1.43Å respectively. (Armstrong and Prout, 1962) showing that there may be a greater degree of delocalisation in this case. Dunitz and Pauling (1960) found that the average single and double bond lengths in the conjugated part of cycloheptatriene molybdenum tricarbonyl were 1.43Å and 1.35Å respectively. These figures suggest even less delocalisation. In the present case, there is doubtlessly alternation in bond lengths, but perhaps not sufficient of it to suggest a complete lack of delocalisation.

The average chromium-carbon bonded distance is 1.85Å which is sensibly in accord with 1.83Å found by Armstrong and Prout in the determination mentioned above, but is considerably lower than the value of 1.92Å found by electron

diffraction methods for chromium hexacarbonyl (Brockway, Ewens and Lister, 1938).

The mean chromium - 'carbonyl' oxygen non-bonded distance, 3.05Å, is in good agreement with the chromium hexacarbonyl result of 3.08Å.

Armstrong and Prout (1962) in the above analysis reported an average value of 2.24Å for the distance between the chromium atom and the unsaturated carbon atoms in the ring. The value obtained in this chromium carbonyl compound is 2.21Å. The chromium - C(10) distance is 2.86Å, showing that the methylene group is on the opposite side of the ring from the metal. Armstrong and Prout's mean value is expectedly larger - 3.19Å. The metal is bonded to the cycloheptatriene ring by means of the overlap of its d-orbitals with the partially delocalised π-electron density.

The mean plane deviations are shown in Table 37. The mean displacement of C(10) and C(10)' from planes (1) and (3), 0.80Å, is highly significant and confirms the conformation found in cycloheptatriene molybdenum tricarbonyl where the deviation was 0.67Å (Dunitz and Pauling, 1960). None of the benzene ring atoms deviate significantly from the mean planes. Both of the benzene rings lie at effectively the same angle to the mean plane through six atoms of the cycloheptatriene ring, and this despite the

fact that there is presumably the possibility of free rotation about the C(10) - C(11) bond.

The mean Cr - C - O valency bond angle is 171° which is in good agreement with the value of 172° of Armstrong and Prout (1962). The corresponding values for the 'carbonyl' C - Cr - 'carbonyl' C bond angles are 91° and 88° respectively.

The average value of an internal valency bond angle in the five-membered ring is 108°. This is in accord with the pattern mentioned in section 2.(9). The cyclopentenone ring includes a double bond and is fused to a quasi-aromatic ring, so that the average bond angle should be about 108°, planarity of the five-membered ring being almost preserved. The mean bond angle in the seven-membered ring is 123° and compares favourably with the value of 125° for cycloheptatriene molybdenum tricarbonyl (Dunitz and Pauling, 1960).

A noteworthy feature of the temperature factors listed in Table 21 is the very high values of U_{11} for the carbonyl oxygen atoms. This is presumably a reflection of the ease of bending of the metal-carbonyl system.

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TABLE 32

Chromium carbonyl compound

Course of structure analysis and refinement.

Operation	Atoms included	R(%)
2D Patterson syntheses	-	-
3D Patterson synthesis	-	-
1st 3D Fourier synthesis	2Cr	55.0
2nd 3D " "	2Cr+35(C)+7(O)	43.8
3rd 3D " "	2Cr+40(C)+10(O)	37.6
4th 3D " "	2Cr+42(C)+10(O)	35.4
Common reflections averaged and unobserved terms omitted	2Cr +42(C)+10(O)	32.6
1st 3D (F_o-F_c) synthesis	2Cr+42(C)+10(O)	30.0
2nd 3D " "	2Cr+42(C)+10(O)	29.5

TABLE 33

Chromium carbonyl compound

Atomic Coordinates and α-values

Atom	x/a	y/b	z/c	$0.35\beta_e$ α	Atom	x/a	y/b	z/c	$0.35\beta_e$ α
C(1)	0.6088	0.3946	0.1463	4.02	C(1)'	0.5286	0.9096	0.3651	4.06
C(2)	0.6467	0.4670	0.0717	3.98	C(2)'	0.6157	0.9804	0.4471	3.93
C(3)	0.6657	0.4121	0.0091	3.83	C(3)'	0.6857	0.9247	0.5193	3.73
C(4)	0.6393	0.2954	0.0198	3.83	C(4)'	0.6501	0.8105	0.4994	4.11
C(5)	0.6388	0.2238	-0.0620	4.03	C(5)'	0.7062	0.7419	0.5629	3.90
C(6)	0.6427	0.1127	-0.0246	4.26	C(6)'	0.6735	0.6272	0.5333	4.29
C(7)	0.6595	0.0651	0.0716	4.28	C(7)'	0.6135	0.5743	0.4289	4.34
C(8)	0.6771	0.1125	0.1694	4.13	C(8)'	0.5757	0.6293	0.3314	4.21
C(9)	0.6689	0.2174	0.1780	4.25	C(9')	0.5700	0.7342	0.3343	4.64
C(10)	0.5862	0.2720	0.1043	3.82	C(10)'	0.5307	0.7900	0.4024	3.97
C(11)	0.4433	0.2141	0.0732	4.03	C(11)'	0.4032	0.7272	0.4115	3.91
C(12)	0.3964	0.1607	0.1495	3.80	C(12)'	0.2953	0.6803	0.3390	4.05
C(13)	0.2704	0.1225	0.1242	4.15	C(13)'	0.1865	0.6305	0.3474	4.58
C(14)	0.1892	0.1280	0.0286	4.41	C(14)'	0.1701	0.6244	0.4409	4.57
C(15)	0.2328	0.1800	-0.0482	4.52	C(15)'	0.2753	0.6675	0.5197	4.12
C(16)	0.3657	0.2286	-0.0228	4.20	C(16)'	0.3911	0.7207	0.5141	4.21
C(17)	0.7332	0.5663	-0.0878	4.07	C(17)'	0.8023	1.0816	0.6282	4.16
C(18)	0.7554	0.5908	-0.1955	3.95	C(18)'	0.9119	1.1130	0.7357	4.02
C(19)	0.9274	0.1590	0.1598	4.39	C(19)'	0.8209	0.6709	0.3446	4.44
C(20)	0.8930	0.2602	-0.0120	4.52	C(20)'	0.9149	0.7577	0.5227	4.33
C(21)	0.8788	0.3495	0.1682	4.26	C(21)'	0.8145	0.8604	0.3680	4.41
O(1)	0.5891	0.4080	0.2268	4.36	O(1)'	0.4541	0.9229	0.2821	4.38
O(2)	0.6935	0.4508	-0.0840	4.01	O(2)'	0.7840	0.9703	0.6095	4.03
O(3)	1.0189	0.1350	0.2098	4.82	O(3)'	0.8584	0.6271	0.2860	4.90
O(4)	0.9510	0.2794	-0.0703	5.27	O(4)'	1.0263	0.7778	0.5727	4.90
O(5)	0.9408	0.4352	0.2112	5.14	O(5)'	0.8339	0.9555	0.3332	4.94
Cr	0.8017	0.2221	0.0892	3.74	Cr'	0.7585	0.7310	0.4267	3.99

TABLE 34

Chromium carbonyl compound

Intramolecular bonded distances (Å)

	Molecule I	Molecule II	Mean
C(1) ... C(2)	1.43	1.38	1.41
C(1) ... C(10)	1.61	1.59	1.60
C(1) ... O(1)	1.21	1.20	1.21
C(2) ... C(3)	1.24	1.36	1.30
C(3) ... C(4)	1.44	1.41	1.43
C(3) ... O(2)	1.43	1.38	1.41
C(4) ... C(5)	1.47	1.34	1.41
C(4) ... C(10)	1.45	1.52	1.49
C(5) ... C(6)	1.49	1.45	1.47
C(6) ... C(7)	1.38	1.45	1.42
C(7) ... C(8)	1.40	1.45	1.43
C(8) ... C(9)	1.39	1.36	1.38
C(9) ... C(10)	1.44	1.45	1.45
C(10) ... C(11)	1.54	1.52	1.53
C(11) ... C(12)	1.39	1.31	1.35
C(12) ... C(13)	1.34	1.29	1.32
C(13) ... C(14)	1.33	1.33	1.33
C(14) ... C(15)	1.37	1.32	1.35
C(15) ... C(16)	1.43	1.36	1.40
C(16) ... C(11)	1.34	1.43	1.39
C(17) ... O(2)	1.42	1.41	1.42
C(17) ... C(18)	1.56	1.55	1.56
C(19) ... Cr	1.84	1.82	1.83
C(19) ... O(3)	1.17	1.24	1.21
C(20) ... Cr	1.96	1.80	1.88
C(20) ... O(4)	1.18	1.21	1.20
C(21) ... Cr	1.82	1.84	1.83
C(21) ... O(5)	1.18	1.27	1.23

TABLE 35

Chromium carbonyl compound

Some intramolecular non-bonded distances (< 4Å)

	Molecule I	Molecule II	Mean
Cr ... C(3)	3.22	3.26	3.24
Cr ... C(6)	2.14	2.20	2.17
Cr ... C(4)	2.25	2.30	2.28
Cr ... C(5)	2.28	2.14	2.21
Cr ... C(7)	2.18	2.24	2.21
Cr ... C(10)	2.84	2.88	2.86
Cr ... C(1)	3.84	3.86	3.85
Cr ... C(8)	2.24	2.16	2.20
Cr ... C(9)	2.25	2.15	2.20
Cr ... O(3)	2.99	3.06	3.03
Cr ... O(4)	3.14	2.99	3.07
Cr ... O(5)	2.99	3.09	3.04

TABLE 36

Chromium carbonyl compound

Valency bond angles

	Molecule I	Molecule II	Mean
O(1)C(1)C(2)	134°	133°	134°
O(1)C(1)C(10)	119	121	120
C(10)C(1)C(2)	107	106	107
C(1)C(2)C(3)	107	109	108
C(2)C(3)C(4)	118	116	117
C(2)C(3)O(2)	126	125	126
C(4)C(3)O(2)	115	119	117
C(3)C(4)C(10)	106	103	105
C(3)C(4)C(5)	121	124	123
C(10)C(4)C(5)	131	132	132
C(4)C(5)C(6)	112	122	117
C(5)C(6)C(7)	135	128	132
C(6)C(7)C(8)	128	125	127
C(7)C(8)C(9)	121	120	121
C(8)C(9)C(10)	129	131	130
C(9)C(10)C(11)	116	113	115
C(9)C(10)C(1)	117	111	114
C(9)C(10)C(4)	103	98	101
C(11)C(10)C(1)	107	110	109
C(4)C(10)C(1)	100	103	102
C(4)C(10)C(11)	117	120	119

TABLE 36 (Contd.)

	Molecule I	Molecule II	Mean
C(10)C(11)C(12)	119°	131°	125°
C(10)C(11)C(16)	119	118	119
C(16)C(11)C(12)	121	111	116
C(11)C(12)C(13)	118	130	124
C(12)C(13)C(14)	124	121	123
C(13)C(14)C(15)	120	113	117
C(14)C(15)C(16)	119	128	124
C(15)C(16)C(11)	119	117	118
O(2)C(17)C(18)	106	106	106
Cr C(19)O(3)	170	167	169
Cr C(20)O(4)	177	167	172
Cr C(21)O(5)	165	177	171
C(3)O(2)C(17)	115	119	117
C(19) Cr C(20)	93	85	89
C(19) Cr C(21)	94	87	91
C(20 Cr C(21)	96	88	92

TABLE 37

Chromium carbonyl compound

Some mean plane deviations (Å)

1) Plane defined by C(4),C(5),C(6),C(7),C(8),C(9)

Atom	Deviation	Atom	Deviation
C(4)	-0.03	C(8)	+0.04
C(5)	+0.05	C(9)	-0.01
C(6)	-0.03	C(10)	-0.75
C(7)	-0.02		

2) Plane defined by C(10) + molecule I benzene ring

Atom	Deviation	Atom	Deviation
C(10)	-0.05	C(14)	-0.01
C(11)	+0.06	C(15)	+0.01
C(12)	+0.04	C(16)	-0.01
C(13)	-0.04		

3) Plane defined by C(4)'C(5)',C(6)',C(7)',C(8)',C(9)'

Atom	Deviation	Atom	Deviation
C(4)'	-0.11	C(8)'	+0.08
C(5)'	+0.14	C(9)'	Nil
C(6)'	-0.04	C(10)'	-0.85
C(7)'	-0.08		

4) Plane defined by C(10)' + molecule II benzene ring

Atom	Deviation	Atom	Deviation
C(10)'	-0.03	C(14)'	-0.03
C(11)'	+0.02	C(15)'	+0.01
C(12)'	+0.01	C(16)'	+0.01
C(13)'	+0.01		

Plane (1) - Plane (2) angle = 74°

Plane (3) - Plane (4) angle = 78°

Table 38 Chromium carbonyl compound

Latest observed and calculated values of the structure factors.